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The 2004 Annual Meeting abstract supplement unites the Journal *SLEEP* and the science of the Associated Professional Sleep Societies in a new and convenient format. As in past years, this special issue will include all abstracts to be presented at the APSS 18th Annual Meeting, June 5-10, in Philadelphia, Pennsylvania. The supplement will provide all members, including those unable to attend the meeting, a brief glimpse into the new ideas and fresh research, which the APSS Annual Meeting provides.

Of the 932 abstracts accepted, 227 will be presented in oral presentation format and the remainder as poster presentations. Similar to the 2003 Annual Meeting, the Program Committee again elected to:

1) Thematically group the posters presented at the meeting;
2) Display posters for one of the three scheduled poster days;
3) Most importantly, there will be a 90 minute block of time each day (Monday, Tuesday, and Wednesday, June 7, 8 and 9) between 1:30pm and 3:15pm that authors will be available for questions during poster viewing.

Each poster will have a unique 3 digit number within the appropriate category (listed below) which should allow for easy identification.

The categories for this year's science have not changed from last year and are listed here:

Category A—Basic Neuroscience
Category B—General Physiology
Category C—Clinical Pharmacology
Category D—Dreams
Category E—Circadian Rhythms
Category F—Phylogeny
Category G—Pediatrics
Category H—Aging
Category I—Sleep Deprivation
Category J—Sleep Disorders - Breathing
Category K—Sleep Disorders - Narcolepsy
Category L—Sleep Disorders - Insomnia
Category M—Sleep Disorders - Parasomnias
Category N—Sleep Disorders - Movement Disorders
Category O—Sleep Disorders - Neurologic Disorders
Category P—Sleep in Medical Disorders
Category Q—Sleep in Psychiatric Disorders
Category R—Instrumentation and Methodology
Category S—Sleep Education
Category T—Molecular Biology and Genetics
Category U—Sleep and Behavior

Attendees of the APSS 18th Annual Meeting will experience a forum for the discussion of new ideas and key research in the field of sleep medicine and sleep research. Our hope is that this experience fosters an environment in which members and attendees obtain education on the latest treatment and technologies in the sleep field, further promoting the recent growth trend in the field. We look forward to sharing in the success of this pivotal event.

David P. White, M.D.
Editor-in-Chief

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001

The Effect of Injection of H-current Blocker in Medial Septum on Hippocampal Theta Rhythm

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Introduction: Theta rhythm, a prominent feature of hippocampal activity during awake exploration and REM sleep, is driven by two major inputs originating from the entorhinal cortex (EC) and medial septum (MS). H-current (Ih) is expressed in projection neurons of both EC (layer II stellate cells) and MS (GABAergic neurons). It was demonstrated in slice that Ih acts as a pacemaker current in the EC and controls the firing rate and bursting frequency of septohippocampal GABAergic neurons in the MS. In this study the role of Ih in MS neurons in the control of hippocampal theta was investigated in in vivo experiments.
Methods: The experiments were conducted in unanesthetized freely moving rats and in rats anesthetized with urethane. In this latter group, hippocampal EEG was recorded and the dynamics of theta and non-theta patterns of activity was monitored and compared in controls and during and after (1 hr each) administration of ZD7822 in the MS using reverse microdialysis (probe 0.24 mm diameter, 1 mm membrane length, rate: 80ul/h) in concentrations of 10uM (n=5), 30uM (n=15), 50uM (n=7), 100uM (n=3), 200 uM (n=1), 300uM (n=2). Theta was also elicited by electrical stimulation of the nucleus pontis oralis at different intensities. Rats for chronic experiments were prepared for standard sleep recordings (EMG, frontal cortical EEG, hippocampal EEG) which started 5-7 days after surgery and lasted for 4-6hrs a day for 3-5 days. The H-current blocker was administered by pressure injection into the MS in doses of 0.2ug, 0.5ug (n=3) and 1.5ug (n=1) after which the rats behavior and hippocampal EEG was monitored for 1 hr in a new environment and for another 4 hrs in their home cage.
Results: Hippocampal theta persisted after blockade of Ih in the MS (doses <200uM) and its appearance followed a natural dynamics, i.e. hippocampal EEG was shifting between theta and non-theta under urethane anesthesia and theta was associated with exploratory behavior and REM sleep in chronic animals. The frequency of spontaneous theta under urethane was between 3-5 Hz in control recordings and remained unchanged after Ih blockade. Ih blockade, however, effectively eliminated high frequency theta elicited by brainstem stimulation (doses 30uM or higher). In intact rats, there was a linear relationship between stimulus intensity and theta frequency whereas after injection of Ih blocker the frequency of theta was constant (3-5 Hz) independent of stimulus intensity. In freely moving rats theta frequency decreased from 7-8 Hz to 5-6 Hz in all theta behaviors.
Conclusion: The present data demonstrate that H-current in MS neurons plays a critical modulatory role in theta generation in vivo. Although low frequency (atropine sensitive) theta can persist after MS Ih blockade, functional Ih is necessary for the MS to generate or transmit high frequency theta elicited by strong ascending activation.

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002

Effect Of Suprachiasmatic Nucleus Lesions On Rat Cerebrospinal Fluid Hypocretin-1 Regulation

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Introduction: Hypocretins-1 and -2 (also known as orexins) are neuropeptides synthesized by lateral hypothalamic neurons. Hypocretins regulate a range of physiological functions including sleep, food intake, autonomic regulation, neuroendocrine secretion and energy homeostasis. A dysfunction of the hypocretin system leads to narcolepsy in humans, rodents and canines. Hypocretin release, as assessed in in vivo dialysis or in cisternal cerebrospinal fluid (CSF), displays rhythmic changes across the 24-hour day. Hypocretin release also increases with sleep deprivation, suggesting homeostatic regulation. We examined the role of circadian factors on hypocretin release by studying suprachiasmatic nucleus lesioned (SCNx) rats.
Methods: We attempted to surgically ablate the SCN of 36 adult male Wistar rats (250 g - 300 g at time of surgery). Thirty sham-operated animals were also used. Animals were implanted with EEG/EMG electrodes and activity/temperature transmitters. Recovery was allowed for 1-2 weeks. Data were collected using SCORE, a computer-based physiological monitoring and data collection system. Animals were housed individually under 3 lighting conditions (12h:12h light:dark cycle (LD), constant light (LL), and constant dark (DD)). Only 19 SCNx animals were found to be arrhythmic in DD for at least 3 weeks, and were retained for further hypocretin analysis. All lesions were verified histologically and shown not to affect hypocretin-containing cells. A minimum of 3 days was permitted between cisternal CSF taps on the same animal. In free running sham-operated animals, CT12 was defined as activity onset. Hypocretin-1 concentrations were determined every 4 hours using radioimmunoassays. Locomotor activity and temperature but not sleep data were analyzed (sleep recordings were available at baseline but not prior to each tap).
Results: Sham-operated animals displayed robust circadian (LL, DD) and diurnal (LD) fluctuations in CSF hypocretin-1, locomotor activity and temperature. Peak CSF hypocretin-1 was at the end of the active period in all conditions. SCNx animals were arrhythmic under LL and DD (temperature and by definition activity). Under LD condition, a weak but significant diurnal fluctuation in activity and temperature was observed. As expected, SCNx rats failed to exhibit circadian hypocretin-1 rhythmicity under LL and DD. Surprisingly, no significant diurnal fluctuation in hypocretin-1 was observed in SCNx animals. We next explored if SCNx affected mean CSF hypocretin-1 and locomotor activity. In constant lighting conditions, SCNx values (CSF hypocretin-1 and locomotion) were intermediate between the peak and nadir of the corresponding non-SCNx values. To study the effect of activity independent of circadian timing, we explored correlations between hypocretin-1 and activity prior to the tap in SCNx rats under constant conditions. Significant correlations between hypocretin-1 and locomotor activity were observed. The best correlations were between -3h to -1h prior to each tap, consistent with CSF fluid dynamics. Significant correlations were observed both across and within animals, suggesting that interindividual and time of day-dependent differences in activity have significant effects on hypocretin release in arrhythmic animals.
Conclusion: This study suggests that hypocretin-1 release is under strong circadian control, and that locomotor activity, either directly or as an indirect reflection of wakefulness, can influence the release of hypocretin-1 into the CSF.

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Hypocretin-1 is under influence of circadian and homeostatic mechanisms

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Introduction: Hypocretin-1 is a recently identified regulator of sleep

and wakefulness and its levels fluctuate with the light-dark cycle. Here we show that rhythmicity of hypocretin is critically dependent on the circadian pacemaker of the suprachiasmatic nucleus (SCN), whereas hypocretin responsiveness to sleep deprivation (SD) is normal after removal of the SCN. The data indicate that circadian and homeostatic mechanisms converge to one single sleep regulatory substance.
Methods: Male rats were subjected to SCN or sham lesioning and were housed under dim red light conditions. Drinking activity records were used to determine the occurrence of arrhythmicity. The animals were implanted with a CSF cannula in the cisterna magna (SCN-lesioned n=21, Control n=16). In order to sample an entire circadian cycle in 2-h intervals, CSF samples were withdrawn every 6-8 h over a 3-day period. The baseline sampling was followed by a 6-h SD. SCN lesions were histologically evaluated after the experiment.
Results: In control animals hypocretin-1 decreased in the beginning of the subjective day, reached lowest levels in the middle of the resting phase (circadian time CT7) and remained low until the start of the active phase. Within 4 hours after onset of activity, hypocretin-1 levels increased and reached maximum levels. The levels between CT7-11 differed significantly from the levels reached between CT23-1 ($p<0.05$ Duncan after sign. ANOVA factor 'time'). In contrast, in the SCN-lesioned group hypocretin-1 showed no circadian pattern over 24 h. Furthermore, hypocretin-1 levels were lower than those obtained in the rhythmic rats ($p<0.0005$, $F=15.465$ ANOVA over 2-h intervals factor 'group'). SD induced a clear increase in hypocretin-1 above the highest level reached during baseline in both groups (Control mean baseline: 869.3 ±36.6, SD: 1205.4 ±51.0; SCN-lesioned mean baseline: 738.3 ±34.3, SD: 1205.2 ±71.5 pg/ml; $p<0.05$, two-tailed paired t-test for both groups).
Conclusion: The data show that the SCN is indispensable for circadian hypocretin rhythmicity. SCN lesions did not affect hypocretin responsiveness to SD, indicating that homeostatic control of hypocretin by sleep is independent of the circadian system. Our finding shows that two relatively independent processes can act on one single sleep regulatory substance.

004

Circadian Behavioral Resetting Through Cholinergic Brainstem Regions Involved In The Sleep-Wake Cycle

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Introduction: Circadian rhythms regulate 24-hour rhythms in phenomena, including feeding behavior and sleep-wake cycles. Mammalian circadian rhythms are regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus. Many neurotransmitters are capable of resetting the circadian clock, including acetylcholine (ACh). Direct application of ACh to the SCN, either in vivo or in vitro, resets the circadian clock in a time-dependent manner, causing only phase advances, with a peak advance in the middle of the night. The physiological context of this signal is unknown, but possible sources of this cholinergic input include the substantia innominata (SI) in the basal forebrain as well as the laterodorsal tegmental nucleus (LDT), pedunculopontine tegmental nucleus (PPT), and parabigeminal nucleus (PBg) in the brainstem. In addition, work from our laboratory has demonstrated that stimulation of either the PPT or LDT in the rat results in an increase in ACh release at the SCN when measured by microdialysis. The SI, PPT and LDT all have been implicated as being important in the sleep-wake cycle, suggesting a possible means by which the sleep-wake and circadian cycles may interact.
Methods: To examine the role of these cholinergic projections in circadian resetting, stimulating electrodes were implanted into either the LDT or PPT of C57Bl/6J mice. Mice were individually housed on running wheels in constant darkness. Under dim red light, subjects were removed approximately 5 minutes before stimulation, gently restrained, and a bipolar electrode cable connected to an electrical swivel was attached to the animal. Mice were stimulated at either circadian time (CT) 6, 14, 20 or 22 (20 mins, 150 uA, 2 msec pulse duration, 10 Hz). Wheel running behavior was analyzed to measure any changes in circadian phase.
Results: Initial results indicate that stimulations of either the LDT or PPT at CT 14 result in significant (~1 hr) phase delays, while stimulations at other time points do not shift the circadian phase significantly.
Conclusion: Stimulation of either the LDT or the PPT is capable of resetting the circadian wheel running behavior of mice in a time-of-day dependent manner. While the projections from the LDT and PPT are primarily believed to be cholinergic, the current behavioral data resembles the phase delay portion of a light response, which would be mediated by glutamate (Glu). Evidence exists for colocalization of Glu and ACh in LDT and PPT projections to the thalamus, so microdialysis experiments are currently underway to determine if Glu is also released at the SCN following PPT or LDT stimulation. Regardless, these experiments provide the first evidence that activation of brainstem regions involved in the sleep-wake cycle results in a functional change in the circadian system. Specifically, LDT/PPT stimulation can reset the circadian clock in the SCN, with this change manifested in a phase-shift in the circadian phase of behavioral rhythms in the animal. This suggests a means by which the sleep state of the animal can feed back to, and reset, the circadian clock.

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005

Local Application of Interleukin-1β Induces Asymmetry in The Slow Wave Sleep EEG

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Introduction: Previously we posited that sleep is a fundamental property of neuronal groups and that such local sleep is dependent upon prior neuronal use. Direct observations supporting this hypothesis indicate that sleep states, as defined by the amplitude of evoked response potentials, are a fundamental property of cortical columns. Further, excessive unilateral sensory input during wakefulness induces EEG asymmetries in subsequent sleep and asymmetry in expression of sleep regulatory molecules. Sleep is regulated in part by a sleep regulatory molecular network including such substances as interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNFα). The synthesis of IL-1β and TNFα are enhanced by neural activity. In view of these findings, we hypothesize that unilateral microinjection of IL-1β onto the cortex would induce localized ipsilateral high amplitude EEG synchronization. In this study, we investigated the effects of IL-1β microinjection on local EEG activities in rats.
Methods: Twenty-four male Sprague-Dawley rats were surgically implanted with an EEG electrode over the somatosensory cortex on both sides on the brain and with a reference electrode over the cerebellum. Two guide injection cannulas whose tips were between the surface of the somatosensory cortex and the dura on each side of the brain were provided. An electrode in the dorsal neck muscles was used to record the electromyogram. All rats were injected unilaterally with 2 μl of pyrogen free saline (PFS) on a control day. The next day, one of the following doses of IL-1β in 2 μl of PFS was injected onto the same side: 1 ng, 10 ng and 50 ng (n=8/group). EEG recordings were recorded for 23 h. The average amount of time spent in each vigilance state was calculated for 3-h intervals. EEG slow wave activity (SWA) during NREMS was cal-

culated. The average of EEG SWA throughout the entire 23 hr control-recording period was normalized to 100% for each animal. Then the EEG power (μV2) for each rat in each 1 Hz frequency band for each side of the brain was determined under baseline conditions (PFS injection) and under experimental conditions.
Results: The duration of NREMS or REMS was not affected by any doses of IL-1β. IL-1β induced EEG asymmetries dose-dependently. The 10 ng or 50 ng IL-1β dose increased EEG SWA during the 0 to 9 h ($P<0.001$) and 0 to 6 h ($P<0.001$) postinjection respectively. The injection of 1 ng IL-1β did not induce EEG asymmetries. The IL-1β induced EEG asymmetries were also state-dependent. The 10 ng IL-1β enhanced EEG power of the 1 to 6 Hz frequency bands only during NREMS ($p<0.001$). During REMS and wakefulness, however, there was no significant difference.
Conclusion: Unilateral injection of IL-1β onto the somatosensory cortex induced ipsilateral dose- and frequency-dependent EEG changes. Maximal responses were state-dependent occurring only during NREMS. Our findings suggest that sleep may begin with state changes occurring within a small part of brain.

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006

Local Application of Tumor Necrosis Factor Alpha Increases Fos and Interleukin-1βImmunoreactivity in the Somatosensory Cortex
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Introduction: Sleep is posited to be a fundamental property of cortical columns or somatosensory barrels (also called neuronal groups). Our hypothesis is that local sleep depends on prior neuronal use. In fact, sleep states of individual cortical columns, as determined by state dependent amplitudes of evoked responses, are, in part, independent of organism sleep. Sleep is regulated in part by a molecular network of sleep regulatory substances that include the cytokines, interleukin-1β (IL1β) and tumor necrosis factor alpha (TNFα). The synthesis of IL1βand TNFα are enhanced by neural activity as well as each other. Dose and frequency and state dependent increases in ipsilateral electroencephalographic (EEG) power occur after unilateral microinjection of TNFα or IL1β onto the surface of the primary somatosensory cortex (SSctx), but not if saline is applied. In this study, we investigated the effects of a unilateral microinjection of TNFα or saline on immunoreactivity for the activity-dependent markers, Fos and IL1β.
Methods: Three male Sprague-Dawley rats (280 to 350 g) received unilateral microinjections of 150 ng of TNFα between the surface of the somatosensory cortex and the dura 3h after light onset. (This dose of TNFα induces EEG asymmetries). The other side was injected with an equivalent volume of saline. The rats were sacrificed 2 h later. The rats were cardiac perfused and brains fixed overnight with 4 percent paraformaldehyde, sunk in 20 percent sucrose and the cortex removed and flattened prior to freezing. Horizontal sections of the cortex (30 μm) were prepared using a sliding microtome and immunoreactivity was performed using primary antibodies against c-fos as well as fos-related antigens (1:2000, Santa Cruz) or rat IL1β (0.3 μg/ml, R&D).
Results: Fos immunoreactive nuclei were evident near (within 1 mm) the microinjection site for TNFα at a much higher concentration than near the microinjection site for saline. Most of the Fos immunoreactive nuclei were evident in the upper layers of the somatosensory cortex. Most of the IL1β immunoreactivity was evident in cells that appeared morphologically similar to astrocytes labeled with glial fibrillary acidic protein. A greater number of IL1β immunoreactive cells were also evident on the side receiving TNFα relative to saline.
Conclusion: The results suggest that cytokine-dependent increases in Fos- and IL1β-immunoreactivity occur in the upper layers of the primary somatosensory cortex with a similar time course to the increases in local EEG synchronization. Current findings are consistent with the hypothesis that sleep may start with changes in a local region of the brain.

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007

Ultradian Sleep Rhythms: Mathematical Model
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Introduction: Mathematical models of sleep have focused either on the biophysics of neural circuits responsible for oscillatory behavior with less than 1 s periodicity (e.g., thalamo cortical circuits generating delta and spindle activity) or on the oscillatory mathematics of the circadian period. Few models address ultradian periods and their underlying neuronal network and cellular mechanisms. A model of ultradian oscillations based on synaptic adaptations to neuronal activity is presented.
Methods: A conceptual model of neuronal-activity-driven synaptic plasticity within a neuronal group, NG, is as follows. 1 - The relationship between NG input (I), μ(t), and NG output (O), α(t), is governed by the net synaptic strength, W(t), in the connection path between I and O. 2) W(t) varies with synaptic strengthening processes (H(t) e.g. Hebbian plasticity) and synaptic weakening processes (S(t) e.g. synaptic scaling). 3) Both H(t) and S(t) increase with NG neuronal activity: H(t) is dependent on correlation, Φαμ(t), between presynaptic and postsynaptic activity; S(t) is dependent on postsynaptic activity alone. Thus, H(t) represents a positive feedback loop Φαμ(t), increases H(t) which strengthens W(t) which increases Φαμ(t). The H(t) positive feedback loop tends to destabilize the NG. In contrast, S(t) represents a negative feedback loop, α(t) increases S(t) which weakens W(t) which decreases α(t). The S(t) negative feedback loop acts to stabilize the NG and will counter the destabilizing actions of the H(t) loop. Thus, synaptic strengthening and synaptic weakening processes are both driven by neuronal activity and they compete to determine the net IO relationship. Can the H(t)-S(t) competition give rise to ultradian oscillations? We couched the conceptual model in mathematical terms and analyzed it for its potential to generate auto-oscillations (i.e., exhibit a limit cycle). The system differential equations describing time variation in H(t) and S(t) were written in the well-known Wilson-Cowan format: dH(t)/dt=-fH(t)+(-bS(t)+hϕ(t))/ square root of ((-bS(t)+hϕ(t))2+1); dS(t)/dt=-gS(t)+(cH(t)+sα(t))/ square root of ((cH(t)+sα(t))2+1) Equation parameters (f, b, h, g, c, s) are critical to whether this system generates oscillatory behavior. Equilibrium points for these equations were established and the Hopf bifurcation theorem was applied to establish the existence of limit cycles and the parameter space in which a limit cycle will occur. Numerical solutions of the differential equations then generated the predicted limit cycle with corresponding period and amplitude.
Results: We found stable limit cycles to exist under the parametric constraints: $g < h < (bc/g)$;$(f = s = 0)$. Under these constraints, the controlling parameter of the oscillatory period is the parameter g, the coefficient governing the rate of decay of S(t).
Conclusion: Competition between synaptic strengthening processes, patterned after Hebbian adaptation, and synaptic weakening processes, patterned after synaptic scaling, gave rise to oscillatory behavior in the IO relation of a NG. The time scale of these oscillations depend on the parameters of the differential equations including those that govern the rate of decay of S(t). If sleep regulating substances, produced by neuronal activity within the NG, are responsible for S(t), then typical time

constants for their decay correspond with a limit cycle possessing a period on the order of an utradian sleep cycle.

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008

Effects Of Nicotinic And Muscarinic Receptor Stimulation At The Hypoglossal Motor Nucleus On Genioglossus Muscle Activity In-Vivo

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Introduction: Suppression of genioglossus (GG) muscle activity in sleep, especially rapid-eye-movement (REM) sleep, predisposes to obstructive sleep apnea but the neural mechanisms mediating such GG suppression are not known. Motoneurons innervating postural limb muscles are actively inhibited in REM sleep by the inhibitory amino acids glycine and GABA. We have recently shown, however, that such inhibitory mechanisms make only a small contribution to the marked suppression of hypoglossal motor output to GG muscle that occurs in REM sleep, suggesting that other, as yet unidentified, neural systems may be more importantly involved. The pontine cholinergic neurons that generate REM sleep also project to the hypoglossal motor nucleus. There is, however, only limited information on the effects of cholinergic stimulation at the hypoglossal motor nucleus on GG activity. Studies using in-vitro tissue slices have shown that acetylcholine excites neonatal rat hypoglossal motoneurons via nicotinic receptors but, in contrast, in juvenile rats it has also been demonstrated that acetylcholine suppresses hypoglossal motoneuron activity via muscarinic receptors. No studies have yet been performed to characterize cholinergic modulation of hypoglossal motor output to GG muscle in an adult preparation in-vivo.
Methods: Urethane-anesthetized, tracheotomized and vagotomized adult rats were studied. Diaphragm and GG activities, blood pressure and the electroencephalogram were recorded. Microdialysis probes were implanted into the hypoglossal nucleus for delivery of cholinergic agonists and antagonists dissolved in artificial cerebrospinal fluid (ACSF), with microdialysis sites verified by histology.
Results: Microdialysis perfusion of acetylcholine into the hypoglossal motor nucleus decreased respiratory-related GG activity with significant effects observed at 0.1mM (decrease to 71.5 ±11.0% of ACSF control, $P<0.05$, n=8 rats). Eserine, an acetylcholinesterase inhibitor, also decreased GG activity (threshold dose 1.0μM, decrease to 63.6 ±11.3% of ACSF control, $P<0.05$, n=6) showing that endogenous acetylcholine modulates GG activity. The suppressant effects of acetylcholine were mimicked with the mixed muscarinic and nicotinic receptor agonist carbachol (threshold dose 0.1μM, decrease to 70.1 ±5.8% of ACSF control, $P<0.05$, n=6). Furthermore, application of 100μM carbachol decreased GG activity to 49.2 ±7.3% of control (n=6) but atropine (10μM) significantly reduced this carbachol-induced GG suppression to 13.8 ±4.0% of ACSF control ($P<0.001$, n=6) indicating that muscarinic receptors contribute to the suppression of GG activity with cholinergic stimulation. In contrast, the nicotinic receptor agonist DMPP increased tonic and respiratory-related GG activity (threshold 1.0mM, $P<0.05$, n=6), i.e. opposite to the effects observed with muscarinic receptor stimulation.
Conclusion: The results show that acetylcholine has mixed effects at the hypoglossal motor nucleus with muscarinic-mediated GG suppression masking nicotinic excitation. Since cholinergic neuronal activity is highest in states of wakefulness and REM sleep it will be important to determine if such nicotinic and muscarinic effects modulate GG activity in a sleep-wake dependent manner.

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009

Caudal Nucleus Tractus Solitarius Involves In The Electroacupuncture-Induced Sleep-Wake Regulation

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Introduction: Electroacupuncture (EAc) is a traditional Chinese Medicine by passing electrical current through needles inserted into acupoints to obtain a variety of therapeutic effects, especially in alleviation of pain and anti-inflammation. The action of EAc also has been demonstrated a sleep improvement for insomniac patients in clinical, however there is lack of scientific evidence to support the EAc effect on sleep regulation. The present study investigated the effects of EAc stimulation of Anmian (extra) acupoints on sleep organization and the implication of a plausibly active structure, the caudal nucleus tractus solitarius (NTS).
Methods: Male Sprague-Dawley rats (250-300 g) were surgically implanted with EEG recording electrodes, and bipolar electrodes used for electrolytic lesion were bilaterally placed in caudal NTS. Rats were allowed a minimum of a one-week recovery period, and kept on a 12:12h Light:Dark cycle at 23 ± 1 °C. After recovery, 24-h baseline recordings were obtained from undisturbed animals and anesthetic effect on sleep was also recorded as control. Rats were subdivided into four groups. Group 1 was subjected to single-administered EAc stimulus. Group 2 received two-administered EAc and subsequently given i.p. muscarinic antagonist, scopolamine prior to the two-administered EAc. Group 3 also received two-administered EAc and then lesion of caudal NTS was executed prior to the two-administered EAc. Group 4 was used to determine the effect of scopolamine or NTS lesion alone on spontaneous sleep-wake activity (the lesion was confirmed by histology). Rats received EAc under anesthetization with inhaled Isoforane (2 %) and oxygen (100 %), and EAc was given prior to the dark onset and lasted for 20-min. EEG recording started at the beginning of dark period and continued for 23-h. There is one-day off between different manipulations in order to avoid accumulation of Isoforane effect and adaptation for EAc stimuli.
Results: Our results show that rats anesthetized with Isoforane produced no change in sleep-wake activity regardless of one- or two-time administration(s) of Isoforane. One-administered EAc+anesthetic did not alter SWS and wakefulness during the dark period comparing with those of anesthetization only, however, REMS significantly increased; the percentage of REMS increased from 2.2 ± 0.5 % to 3.9 ± 0.6 % ($p < 0.05$) in group 1. Both SWS and REMS increased after two-administered EAc+anesthetics, and a mirrored decrease in wakefulness was observed in group 2; the percentages of SWS and REMS increased from 14.7 ± 1.1 % and 1.5 ± 0.3 % to 23.1 ± 1.4 % and 7.0 ± 0.8 %, respectively ($p < 0.05$). Intraperitoneal administration of muscarinic antagonist scopolamine dose-dependently blocked EAc-induced sleep alterations in group 2; SWS and REMS decreased to 12.2 ± 1.2 % and 0.8 ± 0.2 %, respectively, after pretreated with scopolamine. Bilaterally electrical lesion of caudal NTS also blocked the EAc-induced sleep enhancement in group 3; SWS and REMS respectively reduced from 28.6 ± 1.5 % and 7.5 ± 0.3 % after two-administered EAc+anesthetics to 21.5 ± 2.0 % and 2.5 ± 0.4 % after caudal NTS lesion prior to the two-administered EAc+anesthetics ($p < 0.05$). In addition, i.p. scopolamine increased SWS, without change in REMS, on the spontaneous sleep during the dark period in group 4; SWS increased from 23.1 ± 0.5 % to 27.3 ± 1.5 % ($p < 0.05$). This result is consistent with other previous observations. Bilaterally caudal NTS lesion altered neither SWS nor REMS on spon-

taneous sleep during the dark period.
Conclusion: These results provide evidence of EAc effect on sleep regulation, and delineate that muscarinic receptor in the caudal NTS of medulla oblongata may involve in the EAc-induced sleep-wake regulation.

010

GABAergic Neurons of Basal Forebrain and Preoptic Area that Express c-Fos with Sleep Recovery Bear Alpha2 Adrenergic Receptors

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Introduction: Evidence from lesion and other studies has suggested a role of neurons in the basal forebrain (BF) and preoptic area (POA) in promoting sleep, in addition to an important role of cholinergic neurons in the BF in stimulating wakefulness. The sleep-promoting role could be fulfilled by GABAergic neurons that are distributed across these two regions. Moreover, such GABAergic neurons could correspond to those discovered in vitro to be inhibited by noradrenaline (NA). In order to explore this possibility, we examined c-Fos expression following sleep deprivation and recovery in cholinergic and GABAergic neurons of the BF and/or POA. We also employed triple labeling for c-Fos, glutamic acid decarboxylase (GAD) or choline acetyl transferase (ChAT), and alpha2A adrenergic receptors (α2A-AR).
Methods: Male Wistar rats (200-250 g.) were housed individually in cages where they were treated for: 1) total sleep deprivation (SD) by gentle touching for 3 hours, 2) total sleep deprivation for 3 hours followed by sleep recovery (SR) for 3 hours, or 3) natural sleep and waking as sleep control (SC) for 3 hours. At the end of the experimental period at ~1500, they were immediately sacrificed under pentobarbital anaesthesia (100 mg/kg, i.p.). Brains were processed for dual immunohistochemical staining for c-Fos, using black, DAB-Ni as chromogen, and GAD or ChAT using pink, alpha-naphthol pyronin B, as chromogen. Other sections were processed for triple staining for c-Fos using DAB-Ni, ChAT or GAD using green Cy2-conjugated donkey serum and α2A-AR using red Cy3-conjugated donkey serum. Single c-Fos+, double c-Fos+/ChAT+ or GAD+ and triple c-Fos+/ ChAT+ or GAD+/á2A-AR+ cells were mapped and counted using a computer image analysis system equipped for stereological analysis.
Results: The total number of c-Fos+ cells was significantly decreased following SR as compared to SD in the BF and POA across nuclei. Similarly, the proportion of c-Fos+ cells that were cholinergic was significantly decreased in the BF following SR as compared to SD. In contrast, the proportion of c-Fos+ cells that were GABAergic was significantly increased following SR in the BF and POA across nuclei. Finally, the proportion of c-Fos+/GAD+ cells that bore á2A-AR was significantly increased in the BF and POA following SR as compared to SD.
Conclusion: These results provide evidence for the involvement of GABAergic neurons of the BF and adjacent POA in the promotion of sleep, while substantiating the role of cholinergic neurons of the BF in the maintenance of wakefulness. In addition, they suggest that a specific subgroup of GABAergic cells bearing á2-AR is active during sleep. During waking when locus coeruleus neurons discharge and release NA, these GABAergic neurons would be inhibited and subsequently be disinhibited to become active and promote sleep.

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Regional Cortical Metabolism and Dynamics of Slow Wave Activity During Sleep After Unilateral Whisker Stimulation and Sleep Deprivation in Mice

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Introduction: EEG slow-wave activity (SWA, EEG power between 0.75 and 4.0 Hz) in NREM sleep is a marker of sleep homeostasis and a reliable index of NREM sleep intensity. Evidence is accumulating that sleep deprivation (SD) induces differences in the enhancement of SWA within and between the cerebral hemispheres. These topographic EEG differences might reflect neuronal activity-dependent processes. However, it is still unknown whether activity-dependent changes of cerebral metabolism during SD are responsible for the regional gradients of SWA during recovery sleep. We investigated the relationship between regional metabolic activation of the neocortex and cortical EEG during sleep in mice.
Methods: Adult male mice (I/LnJ x C57BL/6) were kept awake for 6 h in an enriched environment after cutting the whiskers on one side to induce unilateral stimulation of the somatosensory cortex. In Experiment 1 DG-uptake was determined in several brain regions including the barrel cortex in 3 groups of mice. DG-uptake was measured in Group 1 (n=9) immediately after the SD, whereas in Group 2 and 3 (n=8, 8) the remaining whiskers were cut after the SD to prevent unilateral stimulation during an additional 2.3 h of enforced waking or recovery sleep respectively, prior to DG-measurements. In Experiment 2 the EEG was recorded bilaterally from a frontal and parietal cortical area during a 24-h baseline and 18 h after the 6-h SD (n=15).
Results: An interhemispheric asymmetry of DG-uptake was found in the barrel cortex immediately after SD, while after additional waking without stimulation or after sleep, the differences between the hemispheres had subsided. In addition, DG-uptake in motor cortical areas was enhanced selectively compared to somatosensory areas. In contrast, the interhemispheric difference in SWA in NREM sleep elicited by the stimulation lasted for 10 h after the SD. Within a hemisphere, the initial increase in SWA was higher in the frontal derivation compared to the parietal derivation.
Conclusion: The data show that the cortical regions with increased DG-uptake after SD correspond to the regions with a larger increase in SWA in subsequent sleep. However, the left-right EEG difference during sleep elicited by unilateral whisker stimulation was prolonged, unlike the transient stimulus-related effect on DG-uptake. An increased functional load may trigger long-lasting processes manifested in the sleep EEG.

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012

Hypocretinergic System And Motor Activity In The Cat

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Introduction: Hypocretinergic neurons in the cat are active during wakefulness when somatomotor activity is present; they are also active during active (REM) sleep induced by carbachol (Torterolo et al., 2001, 2003). In the present report we examined Fos immunoreactivity (as a marker of neuronal activity) in hypocretinergic neurons of the cat during

the waking state in conjunction with different motor paradigms. In addition, as an initial step in exploring the role of dopaminergic neurons in hypocretin-induced motor activation, we analyzed hypocretinergic projections to tyrosine hydroxylase (TH) positive regions known to be dopaminergic.
Methods: Adult cats were maintained for a period of 60-90 minutes preceding euthanasia in one of the following behavioral states: a) quiet wakefulness (QW, n = 3); b) active wakefulness without motor activity, in which the animals were restrained but kept alert with loud clicks (AW w/o M, n = 3); c) active wakefulness with motor-exploratory activity, wherein the animals were freely exploring a new environment and exhibited almost continuous motor activity (AW-ME, n = 3); d) active wakefulness with automatic locomotor activity, in which the animals were habituated to walking on a treadmill (AW-TH, n = 2); e) active wakefulness with motivated locomotor activity (the same as AW-TH), but on the day they were schedule to be euthanized, the animals were presented with the smell and sight of food (AW-TM, n = 3); and f) quiet sleep (QS, n = 4). Actiwatch recordings were obtained during active waking behaviors. After the completion of the preceding paradigms, the animals were euthanized and double immunohistochemical procedures were utilized to detect hypocretin-2 and Fos as well as hypocretin-2 and TH. The number and distribution of hypocretin Fos neurons and the distribution of hypocretinergic fibers were analyzed.
Results: The percentage of hypocretinergic neurons that expressed c-fos was larger during paradigms that included motivated motor activity: AW-ME (79.3% +- 5.0), AW-TM (17.3% +- 2.7); AW-TH (4.8% +- 1.0); AW w/o M (2.3% +- 0.8), QW (1.8% +- 0.9) and QS (0.9% +- 0.6). Statistically greater numbers of cells expressed c-fos during AW-ME compared to all other conditions ($P < 0.001$, ANOVA-Fisher). Larger numbers of c-fos positive cells were present in AW-TM compared to QW, AW w/o M, AW-TH and QS ($P< 0.05$). Anatomical data revealed that a major projection of hypocretinergic fibers is the dopaminergic region in the anterior part of the dorsal raphe nucleus. In contrast, there were very few hypocretinergic fibers in the substantia nigra pars compacta. An intermediate density of hypocretinergic fibers was observed in the ventral tegmental area.
Conclusion: Hypocretinergic neurons are activated during waking behaviors that are associated with motor activity and highly motivated states (AW-ME) compared with comparable motor activity that occurs during less motivated behaviors (AW-TM) or behaviors that lack motivation (AW-TH). Complementary anatomical data reveal that dopaminergic neurons of the dorsal raphe region are likely to be involved in motor activity that is associated with activation of the hypocretinergic system.

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Hypothalamic Contribution to Sleep-Wake Cycle Development
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Introduction: We have recently demonstrated that the hallmark of infant sleep, myoclonic twitching (MT), only occurs against the backdrop of nuchal muscle atonia (NT). Subsequently, we devised a method of identifying sleep states in infant rats using MT/NT as state indicators. Using this method we showed that infant and adult sleep patterns are similar on multiple dimensions, including increased sensory thresholds, brief presence of hippocampal theta, and homeostatical regulation. Infant and adult sleep patterns differ, however, in temporal organization, that is, infants cycle rapidly between sleep and wakefulness and only gradually does a more consolidated pattern develop. Here we use lesions and decerebrations, aimed at disrupting the integrity of structures known to modulate the duration of sleep-wake cycles in adults, to elucidate the neural substrates of sleep-wake consolidation during the first postnatal week in infants.
Methods: Forty-nine 2- to 10-day-old (P2-10) male and female Sprague-Dawley rats were used in a total of 3 experiments. Electrodes were implanted in the nuchal muscle for measuring electromyographic (EMG) activity. Motor behaviors associated with sleep (i.e., MT) and wakefulness (e.g., kicking and stretching) were monitored with a microcamera. Both behavior and EMG were stored synchronously for off-line analysis. In Experiment 1, the duration of sleep-wake cycles was measured in rats at P2, P5, and P8. In Experiment 2, bilateral lesions were placed in the locus coeruleus (LC) in P8 rats and the effects on sleep-wake cycles were measured. Finally, in Experiment 3, P8 subjects were decerebrated either caudal or rostral to the anterior hypothalamus and the effects of sleep-wake cycles were measured.
Results: Sleep-wake cycles of P2 rats were characterized by short periods of muscle atonia and equally short periods of high tone. In P8 rats the sleep periods lengthened significantly and disproportionately in relation to awake periods. Next, LC lesions in P8 rats resulted in rapid cycles similar to those exhibited by P2s; in addition, LC lesions had no effect on awake durations. Finally, transections caudal, but not rostral, to the anterior hypothalamus also reinstated rapid cycling in P8s, again without affecting awake durations.
Conclusion: These results suggest the presence of a bistable mesopontine and medullary circuit governing the sleep-wake cycles that does not include the LC and comes gradually under hypothalamic control during the first postnatal week. This circuit may represent a basic building block with which other sleep components become integrated during ontogeny.

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014

Reduced Extracellular Dopamine in the Striatum of Juvenile Rats Exposed to Intermittent Hypoxia as Neonates
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Introduction: Intermittent hypoxic insults, occurring during a period of critical brain development, lead to locomotor hyperactivity, impaired working memory and altered sleep architecture, with attendant increases in vesicular monoamine transporter and dopamine D1 receptors in the striatum (Decker 2002). These observations led us to hypothesize that persistent and significant impairments in dopamine signaling exist within mesostriatal circuitry of the post-hypoxic rat.
Methods: Twelve male Charles River Sprague-Dawley rats were studied. Following birth, pups were undisturbed and maintained by the dam. On post natal (PN) day 7 pups were randomly assigned to either an intermittent hypoxia-inducing chamber (n=6), or a normoxic chamber (n=6). Between PN 7-11, pups in the hypoxia chamber received 6 hours of intermittent hypoxia per day while pups in the normoxia chamber were exposed to bursts of room air. At the conclusion of the protocol on PN 11, all pups were permitted to mature without further intervention, until weaning at PN 21. Measures of locomotor activity: On PN 35, juvenile rats were placed into cubicles where locomotor activity was continuously recorded over a 72-hour period. Microdialysis: On PN day 40, a guide cannula was surgically implanted into the striatum. Following two days of surgical recovery, rats were placed in a Plexiglas box for a 24 hour adaptation period. Then the guide cannula was removed and a microdialysis probe inserted. Microdialysate collection was initiated and sam-

ples collected at 30 minute intervals over a 50 hour period. Dialysate samples were assayed for dopamine concentration using high performance liquid chromatography electrochemical detection with a reversed phase column.
Results: Post-hypoxic rats traveled significantly further (mean ± SEM centimeters) than control rats during the dark (197.9 ± 9.5 vs 93.1 ± 5.3, $p < 0.001$) phase of the circadian cycle, their typical waking period. There were no differences in total distance traveled during the lights-on phase of the circadian cycle, their typical sleep period. Extracellular levels of dopamine (mean ± SEM picograms in 20 microliters of dialysate) were significantly lower in the striatum of the post-hypoxic rat than the control rat during both the dark (1.33 ± 0.09 vs 2.55 ± 0.12, $p < 0.001$), and lights-on (1.17 ± 0.08 vs 2.66 ± 0.18, $p < 0.001$) phases of the circadian cycle.
Conclusion: We demonstrate locomotor hyperactivity and reduced levels of extracellular dopamine in the striata of juvenile rats exposed to intermittent hypoxic insults between PN days 7-11. These new data, combined with our previous observations, support our hypothesis that intermittent hypoxic insults occurring during a period of critical brain development lead to persistent reductions in dopaminergic signaling within mesostriatal circuitry. We postulate that neonatally occurring hypoxic insults are one pathogenic mechanism contributing to disorders of minimal brain dysfunction, such as attention deficit hyperactivity disorder, characterized by persistent reductions in dopaminergic activity within mesostriatal circuitry.

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015

GABA Release In The mPRF: Role In The Regulation Of Sleep-Wakefulness

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Introduction: The role of medial pontine reticular formation (mPRF) in the regulation of REM sleep is well established. Pharmacological and anatomical studies suggest that the GABAergic neurons of this region may be critical for the regulation of REM sleep. To further investigate the role of GABAergic mechanisms in the regulation of REM sleep, we decided to measure extracellular levels of GABA from the mPRF during spontaneous sleep-wake cycles and during carbachol-induced REM sleep in freely behaving cats. Our working hypothesis was that the GABA release would be lowest during REM sleep as compared with other behavioral states.
Methods: Under standard surgical procedures, male adult cats (~3 Kg) were implanted with standard sleep recording electrodes including LGN electrodes to record PGO activity. Bilateral microdialysis guide cannulas targeted towards the mPRF for later insertion of microdialysis probes were also implanted. After two weeks of post-surgical recovery and habituation in the recording cages, microdialysis probes were inserted. Spontaneous sleep-wakefulness: Following at least 12 hours of post-insertion recovery, behavioral state recording along with artificial CSF (ACSF) perfusion (2 µl/min) and sample collection were begun. A minimum of 2 samples of 6 min each was manually collected during each behavioral state: wakefulness nonREM sleep and REM sleep during spontaneous sleep-wakefulness. The samples were stored in ice until analyzed by HPLC on the same day. Effect of carbachol: The carbachol perfusion experiment was performed following two to three days of sample collections across spontaneous sleep-wakefulness. In this experiment, samples of 6 min each were manually collected during each of the behavioral states with ACSF perfusion. Once the animal had one complete cycle of sleep-wakefulness, carbachol (2mM) perfusion (2 µl/min) was carried out for 30 min to 1 hour and samples were collected during and after carbachol perfusion. HPLC GABA assay: GABA assay was carried out using BAS LC-3C electrochemical detector and standard derivatization protocol. 5 µl of derivatization mixture (3.7 mM o-phthaldehyde and 22 mM 2-methyl-2-propanethiol in 0.01 M borate buffer, pH 9.5) was mixed with 5 µl of microdialysized sample and reacted for 2 min at room temperature before injecting in the HPLC. Using the protocol described above, we were able to achieve a sensitivity of 0.04 pmol/sample.
Results: Initial experiments performed in three cats (three sites) suggest that GABA release in the mPRF was lowest during REM sleep followed by nonREM sleep. The highest levels were observed during wakefulness. GABA levels were also found to be lower during carbachol perfusion as compared with ACSF perfusion.
Conclusion: The preliminary results of our study suggest that GABA levels are lowest during REM sleep as compared with other behavioral states. The results thus indicate that GABAergic mechanisms in the mPRF may be important in control of REM sleep.

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016

Pontine-Wave (P-Wave) Generator Activation-Dependent Memory Processing Involves CA3 Region Of The Dorsal Hippocampus

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Introduction: Activation of the brainstem P-wave generator is critical for REM sleep-dependent memory processing. A functional neuroanatomical study has shown that the P-wave generator cells project to the hippocampus, and other forebrain regions that are involved in memory processing. Based on our earlier studies, we hypothesized that during REM sleep, activated P-wave generator reactivates the hippocampal memory system, aiding in the consolidation and retention of memory. The aim of this study was to identify the possible dorsal hippocampal subfield, involved in the p-wave generator activation-dependent memory processing.
Methods: Experiments were performed on 24 adult male Sprague-Dawley rats, weighing between 200-300 g in accordance with NIH guidelines on the care and use of laboratory animals. To objectively measure states of sleep and wakefulness, rats were chronically implanted with electrodes for sleep recordings. In addition, bilateral stainless steel guide tubes were implanted stereotaxically in the CA3, CA1 fields, or dentate gyri (DG) of the dorsal hippocampus of different animals. After surgical recovery, habituation, and baseline sleep-wake recording sessions (10 A.M. to 4 P.M.), the CA1, CA3, or DG were lesioned by microinjection of ibotenic acid (0.5 µg in 0.05 µl). In the sham lesioned animals, 0.05 µl of saline was injected into these areas. Following microinjection, rats were habituated with the shuttle box for 10 days. For the last three days of those 10 habituation days, sleep-wake recordings were collected to determine the effects of lesions on the sleep-wake cycle. Immediately after the habituation period (day 11), rats were subjected to a session of two-way active avoidance learning training (TWAA) in the morning (between 9:15 and 9:45 A.M.). Immediately after training trials, rats were allowed a six-hour period of undisturbed sleep in the recording chamber. At the end of 6 hrs of undisturbed sleep-wake recordings, rats were tested in a session of TWAA (between 4:05 and 4:50 P.M.).
Results: These lesions in the CA3, CA1 or DG of the hippocampus did not appear to change the sleep-wake cycle. After learning trials, the total

percentage of time spent in REM sleep was significantly higher in the CA3 lesioned animals (36.2% higher), the CA1 lesioned animals (44.3% higher), and in the DG lesioned animals (43.3% higher). In addition, learning trials also increased REM sleep P-wave density in the three lesioned groups (CA3: 53.2%, CA1: 68.16%, and DG: 42.5% higher). In the training session, the avoidance performances of these lesioned groups were comparable to those of the sham lesioned animals. In the test session, avoidance performance was significantly improved in all groups except the CA3 lesioned animals (sham lesioned: 65.7%, $P<0.001$, CA1 lesioned: 74.54%, $P<0.001$, and DG lesioned 66.0%, $P<0.001$). The CA3 lesioned rats failed to show any improvement in the performance during the test trials despite the occurrence of increased REM sleep and increased REM sleep P-wave density.
Conclusion: These findings, for the first time, show that bilateral damage within the CA3 field of the dorsal hippocampus profoundly impairs P-wave generator activation-dependent TWAA memory processing and improvement of learning. Interestingly, bilateral lesioning of the different subfields of the dorsal hippocampus did not interfere with the TWAA trials-induced homeostatic drive for the increased REM sleep and P-wave activity. This evidence supports our hypothesis that during REM sleep, the P-wave generator interacts with the CA3 field of the dorsal hippocampus for the memory processing of TWAA learning.

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017

Pontine Wave Generator Activation-Dependent Learning Training Trials Increases Phosphorylated CREB Immunoreactivity In The Dorsal Hippocampus

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Introduction: The cAMP response element binding protein (CREB), a transcription factor, plays a critical role in long-lasting synaptic plasticity and long-term memory formation. Memory processing of the two-way active avoidance learning (TWAA) depends on the activation of the pontine wave (P-wave) generator. However, the mechanisms of P-wave generator dependant CREB activation during TWAA memory processing are not fully understood. The aim of this study was to quantify the density of CREB activated cells in the dorsal hippocampus after a session of TWAA training trials.
Methods: Experiments were performed on male Sprague-Dawley rats, weighing between 250 and 300 gm in accordance with NIH guidelines on the proper care and use of laboratory animals. After a single session of TWAA trials (30 CS-UCS trials) or control trials, animals were allowed to a three-hour period of undisturbed sleep in the home cage. At the end of this three-hour undisturbed sleep-wake period, animals were deeply anaesthetized with sodium pentobarbital (70 mg/kg, i.p.). Brains were removed after transcardial perfusion of phosphate buffer and then 4% paraformaldehyde in 0.1 M phosphate-buffered saline. The free-floating sections (25-µm thick) were processed for immunocytochemistry to visualize phosphorylated CREB (pCREB) positive cells in the dorsal hippocampus. Sections were then examined using a fluorescent microscope and images were captured using a color CCD camera using Microfire imaging software. Cell counts per unit area of pCREB positive nuclei in the CA1, CA3 fields and dentate gyri (DG) were made in a 2.5 mm2 sample field at equivalent loci in control and experimental animals.
Results: TWAA trials increased activation of CREB as indicated by the increased number of pCREB positive cell nuclei per unit volume in the entire dorsal hippocampus. In the both control and learning groups, the total number of pCREB positive nuclei was greater in the DG than it was in the CA1 and CA3 sub-fields of the dorsal hippocampus. When pCREB cell numbers were compared within the same sub-fields between control and learning groups of animals, the results showed that the learning trials-induced CREB activation was highest in the CA3 sub-field of the dorsal hippocampus (47.79%). The next increase was in the CA1 (35.80%) sub-field of the dorsal hippocampus and then in the DG (17.24%).
Conclusion: These results demonstrate that TWAA leads to increased CREB dependent gene expression in the dorsal hippocampus. The maximum increase of this CREB phosphorylation occurred in the CA3 sub-field. The present findings, together with our previous behavioral and physiological data, support our hypothesis that the TWAA training trials-induced activation of the P-wave generator activates CREB-dependent gene expression in the hippocampus.

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Pontine Wave Generator Activation-Dependent Learning Training Trials Increases Phosphorylation Of CREB In The Dorsal Hippocampus

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Introduction: Data from a series of genetic, biochemical and behavioral studies in Aplysia, Drosophila, Mice and Rats have confirmed that long-term memory formation involves the coupling of gene transcription and protein synthesis. In this regard, the cAMP response element binding protein (CREB), a transcription factor, plays a pivotal role in long-lasting synaptic plasticity and long-term memory formation. Whether the activation of CREB is involved in the pontine wave (P-wave) generator activation-dependent memory processing is not known. Memory processing of two-way active avoidance learning is dependant upon the activation of the P-wave generator (Datta, J. Neurosci. 20:8607-8613, 2000), and thus the aim of this study was to determine the effects of two-way active avoidance learning training trials (TWAA) on the phosphorylation of CREB in the dorsal hippocampus.
Methods: Experiments were performed on 24 adult male Sprague-Dawley rats, weighing between 250 and 300 gm in accordance with NIH guidelines on the proper care and use of laboratory animals. After a single session of TWAA (30 CS-UCS trials) or control trials, animals were sacrificed at three time intervals (1h, 3h, 6h after the end of learning or control trials). The hippocampi were then quickly removed and sonicated at 4°C in an ice-cold lysis buffer. The resulting homogenates were centrifuged and the supernatant was collected to assess the levels of CREB and pCREB using the western blotting technique. For this technique, suitable aliquots of proteins were boiled in sample buffer for 5 minutes, and then resolved on 10% SDS-PAGE gels. The proteins were then transferred to Immun-Blot PVDF membranes by electro-blotting. Membranes were pretreated with blocking buffer and then incubated with anti-phoshphorylated CREB. After incubation overnight and subsequent washing with Tris buffered saline (TBS), the membranes were incubated in a 1:5000 dilution of horseradish peroxidase-conjugated anti-rabbit IgG for two hours. The immuno complexes were detected with a chemiluminescent substrate. The quantification of the immunureactive band was carried out utilizing a Kodak imaging densitometer. To calculate the phosphorylated versus nonphosphorylated form of CREB, the same membrane was stripped with stripping buffer at 70° C for 30 minutes and incubated with anti-CREB and detected as described above.
Results: CREB phosphorylation after a session of TWAA was increased at all three post-training time intervals. This increased level of pCREB

was significantly higher at 3h (59.0% higher, P < 0.001) and 6h (52.5% increase, P < 0.05). In the 1h time interval, pCREB level was higher but, not at a statistically significant level (32.0% higher, p >.05). Thus it appeared from these data that the level of activation reaches a peak at approximately 3 hours post-training.
Conclusion: These results demonstrate that TWAA leads to increased CREB dependent gene expression in hippocampus. The maximum increase of this CREB phosphorylation occurred after three hours. This observation is consistent with our earlier studies in which we demonstrated that the TWAA induced an increase in REM sleep P-wave density peaks at three hours. The present findings, together with our previous behavioral and physiological data, supports our hypothesis that the activation of the P-wave generator acts as a brainstem switch to trigger CREB-dependent gene expression and protein synthesis in the hippocampus for the consolidation of TWAA memory.

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019

The Efferent Neural Projections From A Putative Sleep Promoting Area Of The Brain, The Median Preoptic Nucleus

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Introduction: The preoptic area is critically implicated in the regulation of sleep. The median preoptic nucleus (MnPO) is located midsagitally, at the anterior wall of the third ventricle and contains numerous GABAergic sleep-active neurons. Activation of these neurons may promote nonREM sleep by innervating wake-promoting sites within the brain. Additionally, these GABAergic sleep-active neurons may also be warm-sensitive. Therefore, the efferent projections from the MnPO were studied with the use of the anterograde tracer, biotin dextran amine (BDA). Fluorescent latex microspheres or fluoro-gold were also used in combination with Fos immunohistochemistry to identify putative warm sensitive neurons that project to specific regions of the brain.
Methods: Anesthetized rats were fixed in a stereotaxic frame, a hole was made in their skulls and the animals were pressure injected with BDA (5% in isotonic saline) or retrograde tracer dorsally using a micropipette. Animals were allowed to recover and 11 or 4 days following the injection of BDA or retrograde tracer respectively, they were then killed by an anesthetic overdose and transcardially perfused. Their brains were cut into 40um coronal sections and processed for the visualization of tracer substance. Fos immunohistochemistry was performed on brains that had prior injections of retrograde tracer into the perifornical lateral hypothalamus (LHA), the parvicellular part of the paraventricular nucleus of the hypothalamus (pPVH) or the periaqueductal gray (PAG). Fos was identified within the MnPO following increased ambient temperature (39oC for 60mins) by the nickel-diaminobenzidine technique.
Results: Numerous efferent neural projections with boutons or varicosities were identified within the brain following the application of the anterograde tracer BDA. These areas included the organum vasculosum of the lamina terminalis, the subfornical organ, the supraoptic nucleus, the medial preoptic area, the anteroventral preoptic nucleus, the anterior hypothalamic nucleus, the medial and lateral septal nuclei, the LHA, PVH, the zona incerta, the dentate gyrus, the anterior cingulate cortex, the PAG, and the coerulear/ pericoerulear area. Neurons that were activated (indicated by the presence of Fos) within the MnPO that projected to the LHA, the pPVH or the PAG in response to heat exposure were significantly increased over control values. Activated neurons within the MnPO that projected to the perifornical LHA were greater in number that those that projected to the pPVH or the PAG.
Conclusion: The efferent neural projections from the MnPO indicate it may have roles in fluid homeostasis, autonomic responses and arousal. Efferent projections to the LHA, the dentate gyrus, the coerulear/pericoerulear area and the septal region indicate that the MnPO may be able to modulate a number of significant wake related regions of the brain. Activated neurons within the MnPO following increased ambient temperature significantly project to the perifornical LHA area. This may promote nonREM sleep by innervating wake-promoting neurons within this part of the brain, as GABAergic sleep-active neurons may be warm-sensitive.

020

Inhibition of Caspase-1 Inhibits Spontaneous Non-Rapid Eye Movement Sleep of Rats

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Introduction: Mature and biologically active interleukin (IL)-1β is cleaved from a prohormone by a cysteinyl aspartate-specific protease (caspase)-1, originally termed IL-1β converting enzyme (ICE). Evidence suggests that IL-1b is involved in physiological NREM sleep regulation. This study aimed to test the hypothesis that interfering with the cleavage of mature IL-1β from its inactive precursor would reduce NREM sleep of rats. To this purpose freely behaving rats were administered the caspase-1 inhibitor Ac-YVAD.cmk (Ac-Tyr-Val-Ala-Asp chloromethyl ketone) at the beginning of the light (rest) phase of the light-dark cycle and subsequent effects on spontaneous sleep were determined.
Methods: Ac-YVAD.cmk was dissolved in 0.6% dimethylsulfoxide (DMSO) in pyrogen-free saline (PFS). Male Sprague-Dawley rats (n=12), maintained on a 12:12 h light:dark cycle at 22 °C, were instrumented for standard chronic polygraphic recordings of sleep-wake activity. After recovery and habituation to the recording conditions, these animals were injected intracerebroventricularly at light onset with 1 µl vehicle (0.6 % DMSO in PFS) and 3, 30, 300 and 1500 ng Ac-YVAD.cmk. Injections were made at least 4 days apart.
Results: The amount of time spent in non-rapid eye movement (NREM) sleep during the 12-h postinjection light period was reduced from an average of 53.5 ± 1.4 % of recording time after vehicle to 46.2 ± 2.0, 49.1 ± 1.8, 42.5 ± 1.8 and 44.8 ± 1.9 after 3, 30, 300 and 1500 ng Ac-YVAD.cmk, respectively. This reduction in NREM sleep was mirrored by an increase in wakefulness (from 35.6 ± 1.5 % of recording time after vehicle to 45.5 ± 2.4, 39.6 ± 2.1, 47.4 ± 1.7 and 44.9 ± 2.3 after the four different Ac-YVAD.cmk doses administered, respectively). These alterations in NREM sleep and wakefulness were not followed by any compensatory rebound in post-injection hours 13 -23 (corresponding to the dark period). The power spectrum of the EEG delta band (slow wave activity, SWA) during NREM sleep was reduced from an averege of 2622 ± 88 mV2/Hz after vehicle to 1944 ± 119, 1695 ± 97, 2035 ± 120, 1991 ± 107 after the four different Ac-YVAD.cmk doses administered, respectively. This reduction in SWA activity persisted during post-injection hours 13 -23. Rapid eye movement sleep and brain cortical temperature were not affected by any of the Ac-YVAD.cmk doses administered, in anytime interval.
Conclusion: The results show that interfering with the cleavage of mature IL-1β from its inactive precursor reduces NREM sleep of rats, at the expense of wakefulness. These data support a role for IL-1β in the regulation of spontaneous, physiologic NREM sleep. The results of this study also suggest that IL-1β i) may play a role in the physiologic regu-

lation of SWA during NREM sleep, ii) is not involved in the physiologic regulation of REM sleep, and iii) although it plays a key role in fever, it is not involved in physiologic thermoregulation.

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Differential Effects of Lorazepam on Sleep Architecture in C57BL/6J (B6) and BALB/cJ (C) Strain Mice

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Introduction: Compared to the B6 strain, C mice exhibit greater "anxiousness" on behavioral tests of anxiety, and can show significantly longer sleep disruptions after exposure to anxiogenic situations. Relative to B6 mice, C mice also have been reported to have fivefold less benzodiazepine (BZ) receptor density in the amygdala, a region important in anxiety and in the control of arousal, but similar BZ receptor densities in other brain areas. Lorazepam is a BZ receptor full agonist that has been used to treat both anxiety and insomnia. Differences between B6 and C mice raise the question of whether BZs would differentially impact sleep in the two strains. In this study, we examined the effects of lorazepam on sleep and activity in B6 and C mice.
Methods: The subjects were B6 (n=8) and C mice (n=8) obtained from Jackson Laboratories. The mice were surgically implanted with transmitters for recording activity and sleep via telemetry. After recovery from surgery, sleep was recorded for 22 h following I.P. injections of two dosages of lorazepam (L: 0.5 mg/kg; H: 1.5 mg/kg) or saline alone (0.2 ml). Injections were administered in a counterbalanced order at one-week intervals. Activity and sleep data were analyzed in two 5-h segments (blocks 1-2) in the light period and two 6-h segments (blocks 3-4) in the dark period. Comparisons among means were conducted with paired t-tests ($p < 0.05$).
Results: Compared to saline, both L and H dosages of lorazepam produced significant reductions in activity and increases in NREM in blocks 1-4 of B6 mice and in blocks 1-3 of C mice. In both strains, the largest decreases in activity and increases in NREM occurred in block 3 with no significant dosage effect within strains. In B6 mice, REM was increased in blocks 2-4 after L and in block 3 after H. In C mice, L had no significant influence on REM, whereas REM was significantly reduced in blocks 1-2 after H.
Conclusion: The results demonstrate significant differences between B6 and C mice in the effects of lorazepam on REM, whereas the effects on NREM and activity were similar. Strain differences in the number of BZ receptors in the amygdala, but not in other brain regions, suggests possible site specificity in the effects of lorazepam on REM. This conclusion is also suggested by recent work demonstrating a significant modulatory role of the central nucleus of the amygdala on REM.

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Regional Fos and Zif268 Expression Associated with Restraint-Induced Increases in REM in C57BL/6J (B6) Mice

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Introduction: Restraint stress administered to rodents in the light period is followed by a subsequent significant increase in REM sleep in the dark period when the animals are typically active. Fos and Zif268 are often used to identify "activated" neurons in association with behavioral phenomena. In this study, we utilized Fos and Zif268 immunomapping procedures to determine brain regions potentially involved in restraint-induced increases in REM in a commonly used mouse strain.
Methods: During the 4th h after lights on, male B6 (n=6) were placed for 1 h in a plastic cylinder (2.5 x 2.5 x 8.0 cm) that limited movement. A separate group of mice was kept awake by gentle handling (n=6) for 1 h on the same schedule as those in the restraint condition. All mice were perfused at the 13th h after restraint (time of greatest REM increase in sleep recorded B6 mice). Brains were sectioned, and immunostained with Fos and Zif268 in alternating sections taken in brainstem, hypothalamic, thalamic and forebrain regions. Digital photographs were taken and Fos and Zif268 positive cells were counted with Metamorph Image Analysis software. Fos and Zif268 counts were expressed as num/mm2 and compared between groups with independent t-tests.
Results: Fos expression in both controls and restrained mice was low, but significant between groups differences were found in several brain regions. Compared to controls, Fos expression in restrained mice was decreased in various subregions of the hypothalamus, in the central grey and in the dorsal raphe nucleus (DRN). Fos was increased in the lateradorsal tegmental nuclei (LDT) and in the anterior paraventricular thalamus (PVT). In both conditions, Fos expression in the locus coeruleus (LC) was not sufficient for analysis. Zif268 was highly expressed in the cortex, amygdala and septal-hippocampal regions in control and restrained mice. The only region with a difference between conditions was the dentate gyrus (DG). Zif268 was only modestly expressed in DG in both groups, but expression was significantly greater in restrained mice.
Conclusion: Restraint produces significant increases in REM at times in which mice would normally be awake and active. Fos patterns in the brainstem (increased Fos in LDT, and decreased Fos in DRN and negligible Fos expression in LC) in association with restraint-induced increases in REM correspond to current notions regarding the roles of these regions in generating and regulating REM. Increases in Zif268 expression in DG complements reports of Zif268 up-regulation in hippocampus in association with increased REM. The only other region in which we observed significantly increased Fos in restrained mice was PVT, though interestingly, circadian Fos expression is reportedly normally greater in PVT at times of day when the animals are most active.

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Cortical Projections Of Rat Basal Forebrain Neurons: Lack Of Axonal Collateralization And Similar Topography Of Cholinergic And Noncholinergic Projections

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Introduction: The basal forebrain (BF) is the major source of extrathalamic projections to the cerebral cortex consisting of cholinergic and noncholinergic components. The cholinergic corticopetal projections have often been suggested to activate the cortex in a diffuse and global manner (Sarter & Bruno, 1997). However, there is also evidence for sensory modality-specific, differential activation of cholinergic corticopetal projections (Zaborszky et al., 1999; Golmayo et al., 2003) which might play a role in attention and plasticity (Rasmusson, 2000). One critical issue in evaluating these opposing hypotheses is the degree of axonal branching of cholinergic afferents within the cortex. Earlier studies reported that

such branching is limited, but more sensitive tracers have since become available. Further, there is little information on the terminal fields of non-cholinergic afferents from the BF which might also play a role in cognitive functions. Using two highly sensitive retrograde tracers, the present study aimed to reinvestigate whether corticopetal BF projections are specific or diffuse with respect to their cortical targets, and to determine whether the degree of axonal branching varies according to the transmitter phenotype of BF neurons.
Methods: Four functionally different cortical regions were selected for investigation: the medial prefrontal, somatosensory, auditory, and visual cortices. Various combinations of two regions were injected with fluorescent retrograde tracers (Alexa 488- and Alexa 594-conjugated cholera toxin subunit B) in each rat. After 7-9 day survival, the rats were perfused and their brains were processed for immunofluorescence using AMCA-conjugated secondary antibodies, for vesicular acetylcholine transporter (VAChT), glutamic acid decarboxylase, and peptide markers present in BF neurons. The distributions of retrogradely labeled BF neurons with or without the immunolabels were examined.
Results: Neurons retrogradely labeled from each of the four cortices were widely distributed across the BF, yet topographic organization was obvious as reported previously. The highest concentration of neurons labeled from the visual cortex was located rostrally in the BF, at the horizontal limb of the diagonal band, followed caudally by peak concentrations of neurons labeled from the medial prefrontal cortex and then the somatosensory cortex. Neurons labeled from the auditory cortex were concentrated most caudally, in the caudal basal nucleus. We found no BF neurons that were double-labeled with the two tracers in any of the injection combinations. The proportion of retrogradely labeled BF neurons that were VAChT-positive varied according to cortical injection sites: 20-30% for medial prefrontal; 60-90% for somatosensory; ~60% for auditory; and 50-60% for visual cortex. Of the retrogradely labeled neurons, heavily labeled neurons had a consistently higher probability of being VAChT-positive than lightly labeled neurons. Cholinergic and noncholinergic, lightly and heavily retrogradely labeled neurons were all co-distributed throughout the BF.
Conclusion: The observed topographical organization of the BF projections, along with the absence of double labeled cells from retrograde tracer injections, suggests that the both cholinergic and non-cholinergic cortical projections from the BF are organized specifically with respect to their cortical targets. The projection patterns of neurochemically-specific non-cholinergic BF neurons are currently under investigation.

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The Effects of Nicotine Withdrawal on Sleep in the Rat

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Introduction: A major symptom of nicotine withdrawal (smoking cessation) is sleep disturbance, including frequent awakenings from sleep and reduced sleep time. Sleep disturbance and the ensuing daytime drowsiness can aggravate or induce other symptoms of nicotine withdrawal such as depression, anxiety, and lack of mental focus. Current smoking cessation therapies such as nicotine replacement or treatment with the antidepressant bupropion can negatively affect sleep as well. The goal of the present study is to determine the whether sleep disturbance occurs in a rodent model of nicotine withdrawal.
Methods: Male Wistar rats (300-350 g) were surgically implanted with skull and muscle electrodes to record electroencephalographic (EEG) and electromyographic (EMG) activity. Following recovery, baseline EEG and EMG data were recorded for 5-7 days. Osmotic minipumps (Alzet 2ML2) were used to deliver continuous nicotine infusion (or vehicle control). The nicotine was placed in an external coil of polyethylene tubing attached to the osmotic pump at the proper volume for a 7-day infusion period. Minipumps containing either nicotine (tartrate salt; Sigma Chemicals; 9 mg/kg/d) or vehicle (sodium bitartrate; Sigma; also 9 mg/kg/d) were surgically implanted in the subcutaneous space between the scapulae. EEG and EMG data were continuously recorded for 14 days, through the 7-day nicotine infusion and the 7-day nicotine withdrawal periods and scored in 10 s epochs as either waking (W), non rapid-eye movement (NR) sleep or rapid-eye movement (R) sleep. Data were analyzed to determine time spent in each state (W, NR, or R) and the mean bout duration for each state. Six 24-h days of recording were analyzed including: baseline, early infusion (day 2 of infusion), mid-infusion (day 4), late infusion (day 6), early withdrawal (day 8), and late withdrawal (day13). Separate analyses were performed for the 12-h light period (7AM to 7PM) and the 12-h dark period (7PM-7AM).
Results: The results of analyses indicate that during the infusion period, increased W bout duration was observed during the dark (active) period in the nicotine-infused group. During the nicotine withdrawal period, we found a 30% increase in NR sleep and a 15% decrease in W during the dark period ($p < 0.05$) and also a 40% decrease in W bout duration in the dark period ($p < 0.05$) in the nicotine-infused group as compared to vehicle controls.
Conclusion: These results indicate sleep disturbance occurs during nicotine withdrawal. Further experiments will determine whether a longer infusion period will result in greater sleep disturbance. The establishment of a model of sleep disturbance during nicotine withdrawal will allow the investigation of neural changes occurring during nicotine addiction and withdrawal that result in sleep disturbance. Furthermore, establishing this model will aid in development of potential smoking cessation therapeutics. We hypothesize that ameliorating the sleep disruption during nicotine withdrawal will alleviate many withdrawal symptoms and increase the rate of successful smoking cessation.

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025

Effects Of Lateral Hypothalamic Lesions With The Neurotoxin Hypocretin2-Saporin On Basal Forebrain Adenosine Levels

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Introduction: The human sleep disorder narcolepsy is now considered a neurodegenerative disease, as there is a massive decrease in number of neurons containing the neuropeptide hypocretin (HCRT), also known as orexin (Nishino et al. Lancet 355: 39, 2000). HCRT neurons are localized only in the perifornical region of the lateral hypothalamus (LH) from where they project to major arousal centers. However, it is not known which projection produces what symptom of narcolepsy. One target site is the basal forebrain and it is possible that waking might be due to the HCRT neurons projecting to the BF and activating the cholinergic neurons. As a result of the HCRT activation of the BF, there should be a congruent increase in local sleep factors such as adenosine (AD); lesion of the HCRT neurons should produce a corresponding decrease in AD and increased sleep. Here we test this pathway by measuring AD levels and sleep in rats with lesions of the HCRT neurons.
Methods: Animals and surgery: Sprague-Dawley rats (280-300g) were administered (under deep anesthesia) either saline (control group) or the

neurotoxin HCRT2-SAP (90ng/0.5µl) into the LH. CSF collections: CSF was collected from all rats at CT0 (36 and 60 days post-lesion) and CT8 (40 and 64 days post-lesion) in randomized order. On day 70 CSF was collected at CT6 in all rats to serve as a baseline for the total sleep deprivation study. On day 77 the rats were kept awake for 6h (first six hours of light period) and CSF was collected. HCRT was detected using RIA as described previously (Nishino et al. Neurology 61: 823, 2003) Microdialysis and sleep recordings: After collecting the CSF, the rats were implanted with sleep recording electrodes and a microdialysis guide cannula into the BF (A= -.35; L= 2.0; H= 8.5 [Paxinos and Watson, 1986]). Microdialysis sampling procedure: Seven days post-surgery, a microdialysis probe was inserted (BAS 1mm length). ACSF was perfused (flow rate=0.25µl/min) and after 24h of stabilization period, samples (5µl) were collected for 2h and then the rats were kept awake for 6h. The rats were then allowed to sleep undisturbed. Microdialysis samples were collected every hour during the 6h prolonged waking and during 2h of recovery sleep. AD levels were determined using HPLC and UV-116A.

Results: The sleep records are still being analyzed but the HCRT and AD analysis is complete. At CT0 and CT8, lesioned animals (n=38) had a significant decline in HCRT levels compared to saline rats (n=19) ($p< 0.0001$). Six hours of prolonged waking increased HCRT levels in saline but not in lesioned rats ($p<0.05$). AD levels were significantly lower in lesioned (n=5) compared to saline (n=9) animals ($p<0.05$). In response to 6h prolonged waking there was a significant increase in AD in the saline rats ($p<0.05$) but not in lesioned rats.

Conclusion: Anatomical studies have shown a unilateral HCRT projection to the BF and here we find that it also drives AD levels. Accumulation of AD in the BF as result of this HCRT activation might then serve to gradually inhibit the BF neurons and promote sleep.

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Interactions between Interleukin-6 and Tumor Necrosis Factor in Sleep and Body Temperature Responses of Mice to Lipopolysaccharide Injection

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Introduction: Sleep-wake behavior is altered in response to immune challenge. The pro-inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF) are two critical mediators of infection-induced alterations in sleep, but other cytokines may also be involved in these responses. In this study, the role of IL-6 in sleep and body temperature responses to immune challenge was investigated by using lipopolysaccharide (LPS) injection into IL-6-deficient mice to mimic aspects of bacterial infection. Neutralizing anti-TNF antibodies were also used to study potential interactions between IL-6 and TNF during these responses.

Methods: C57BL/6J (B6) and B6.129S6-Il6tm1Kopf (IL-6 KO) mice (Jackson Labs) were maintained on a 12:12 h L:D cycle at 29°C. Transmitters (DSI ETA F20) were surgically implanted to measure core body temperature and the electroencephalogram (EEG). Activity was monitored with infrared motion detectors. Vehicle or 10 ug LPS (Sigma Chemicals) was injected intraperitoneally (IP) 15 min prior to dark onset. A separate group of mice was implanted with both transmitters and intracerebroventricular (ICV) guide cannulas. On separate days, these mice received either vehicle ICV and vehicle IP; 10 ug goat-anti-mouse TNF antibody (R&D Systems, Inc.) ICV and vehicle IP; or 10 ug goat-anti-mouse TNF antibody ICV and 10 ug LPS IP 30 min prior to dark onset. Polygraphic signals were digitized and stored for subsequent determination of arousal state.

Results: IP LPS alone: LPS induced fever in B6 mice (peak magnitude: 1.2 ± 0.2°C). In contrast, IL-6 KO mice responded to LPS with a profound hypothermia (peak magnitude: -4.7 ± 0.9°C). LPS increased non-rapid eye movements sleep (non-REMS) relative to control values to a greater degree for B6 (30 ± 4%) than for IL-6 KO (16 ± 6%) mice during the initial 12-h post-injection period. LPS abolished REMS of both strains for 8-9 hours. ICV anti-TNF alone: No significant alterations in body temperature, non-REMS, or REMS were noted following ICV administration of neutralizing anti-TNF antibody. ICV anti-TNF + IP LPS: 10 ug neutralizing anti-TNF antibody markedly attenuated the hypothermic response of IL-6 KO mice to LPS (peak magnitude: -1.6 ± 0.3°C). The increase in non-REMS of IL-6 KO mice after LPS was more pronounced with co-administration of anti-TNF (21 ± 8%). REMS inhibition was unaffected by anti-TNF.

Conclusion: These results support the conclusion that IL-6 influences sleep and temperature responses to immune challenge. LPS induces hypothermia instead of fever in IL-6 KO mice, and this hypothermia can be blocked by anti-TNF neutralizing antibodies. These temperature responses suggest that in genetically intact mice, IL-6 induces fever in response to LPS and inhibits the cryogenic effects of TNF. The non-REMS response of IL-6 KO mice is similar to that of controls when hypothermia is blocked, suggesting that strain differences in sleep responses to LPS may be secondary effects due to cold inhibition of non-REMS.

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Different Discharge Patterns Of Medial Medullary Motor-Related Neurons During Tonic Immobility And REM Sleep

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Introduction: The oral pontine reticular nucleus (PnO) and gigantocellular reticular nucleus (Gi) are main elements of the brainstem-reticulospinal inhibitory system, which hyperpolarize spinal motoneurons during REM sleep. On the other hand, neurons within the PnO and Gi are involved in regulation of tonic immobility (TI) in rodents (Klemm, 1971) and cataplexy in narcoleptic dogs (Siegel et al., 1992). In the current study we investigated discharge patterns of identified Gi neurons related to motor activity (GiMNs) across sleep waking cycle, during TI and PnO electrical stimulation.

Methods: Experiments were performed in freely moving and anesthetized (pentobarbital 50 mg/kg, i. p.) rats. EEG and EMG electrodes were implanted aseptically for polygraphic determination of the sleep-waking states. GiMNs were identified using 4 criteria: (1) short latency orthodromic spikes during stimulation of the contralateral motor cortex (MC), (2) inhibition during PnO electrical stimulation producing behavioral arrest, (3) unresponsiveness to mechanical skin stimulation, and (4) cell activation preceding neck EMG phasic activity. TI in rats was induced by grasping the skin on the dorsal surface of the neck and lifting the animals into the air. Reticulospinal motor-related Gi neurons (RSGiMNs) in anesthetized rats were identified antidromically by electrical stimulation of the spinal cord (SpC) at L2 level.

Results: Sixteen identified GiMNs were analyzed in freely moving rats during the sleep-waking cycle and TI. GiMNs showed a slow firing rate 6.2±1.0 sp/s in quite waking and 5.7±1.5 sp/s (n=16) in slow wave sleep.

During active waking and REM sleep, GiMNs had firing rates of 27.8±2.7 sp/s and 32.8±4.0 sp/s, respectively. During TI, GiMNs showed a firing rate (2.2±0.3 sp/s, n=16) significantly less than the rate in quiet waking (df=15, p<0.0001) and slow wave sleep (df=15, p<0.05). Moreover, the increase of GiMNs firing rate induced by MC stimulation was reduced during TI. Similarly, PnO electrical stimulation (30-150 Hz, 0.2 ms, 50-200 μA) decreased both spontaneous (91±2%, df=15, p<0.0001) and MC stimulation induced (86±4%, df=15, p<0.0001) GiMN activity but did not evoke muscle atonia. Forty two RSGiMNs were analyzed during electrical stimulation of the PnO inhibitory sites and neck squeezing in anesthetized rats. Electrical PnO pulses preceding SpC and MC pulses inhibited both antidromic and orthodromic responses of RSGiMNs in anesthetized rats. The average means for latency and duration of RSGiMNs inhibition were 6.4±0.5 ms and 35.8±3.9 ms (n=8) for antidromic spikes and 5.9±3 ms and 52.5±5.2 ms (n=11) for orthodromic spikes, respectively. Squeezing the skin on the dorsal surface of the neck also reduced spontaneous and MC stimulation induced firing rates of RSGiMNs in anesthetized animals.
Conclusion: Motor-related Gi cells decrease firing rate from active waking to quiet waking, slow wave sleep and TI, but increase their activity in REM sleep. This discharge pattern is similar to the discharge characteristics of movement-related brainstem cells across S-W cycle and cataplexy in narcoleptic dogs. Both artificial (electrical stimulation of PnO inhibitory sites) and natural somatosensory stimuli inducing TI in animals block the descending excitatory influences addressed to spinal motor centers from rostral motor structures at brainstem level.

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Afferents To The Orexin Neurons

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Introduction: Neurons containing orexin/ hypocretin are located in the lateral hypothalamic area (LHA) and perifornical area (PeF), with a few orexin cells extending into the dorsomedial nucleus of the hypothalamus (DMH). These cells send axons to many brain regions, including nuclei governing sleep/wake behavior, feeding, and autonomic function. However, few afferents to the orexin neurons are known.
Methods: To identify pathways that may influence the activity of the orexin neurons, we first microinjected the retrograde tracer cholera toxin B (CTb, 6-9 nl, 1% in PBS) into the LHA, DMH, and PeF area of Sprague-Dawley rats. We also injected the anterograde tracer biotinylated dextrans (BD, 10-20 nl, 12.5% in PBS) into regions identified by retrograde tracing. One week later, animals were perfused with saline and formalin. Brains were sectioned at 40 μm and immunostained for BD, CTb (goat anti-CTb, 1:100k), and orexin (rabbit anti-orexin, 1:3k). Fibers and cells were labeled with DAB (brown), DAB/Ni/Co (black) or Vector SG kit (blue). We also immunostained sections for monoaminergic markers to characterize further those inputs to the orexin neurons.
Results: Retrograde tracing identified heavy inputs to the orexin field from the infralimbic cortex, nucleus accumbens shell, lateral septum, bed nucleus of the stria terminalis, preoptic area (especially in the median, medial, and ventrolateral preoptic areas), the amygdala (especially the lateral, central, and basolateral nuclei), the ventromedial hypothalamus, DMH, lateral/ posterior hypothalamus, tuberomammillary nucleus, dorsal raphe, substantia nigra, periaqueductal grey, lateral/ medial parabrachial nucleus, and raphe magnus nucleus. Anterograde tracing showed heavy inputs to the orexin neurons from the DMH, lateral septum, and bed nucleus of the stria terminalis. In contrast, projections were light from the amygdala, infralimbic cortex, ventrolateral preoptic area, nucleus accumbens shell, nucleus accumbens core, and substantia nigra. Serotonergic and noradrenergic inputs to orexin neurons were strong to moderate, but histaminergic appositions were extremely sparse.
Conclusion: Retrograde tracing, anterograde tracing, and double-label immunohistochemistry shows that the orexin neurons are innervated by regions involved in the control of behavioral state, appetite, emotions, and autonomic function. The heavy projections from the DMH, lateral septum, and medial bed nucleus may be among the most influential.

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Selective Serotonin 5-HT2a Inverse Agonists Promote Sleep Consolidation In Male Wistar Rats During the Normal Inactive Phase

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Introduction: Serotonin 5-HT2 antagonists have demonstrated the ability to enhance slow-wave-sleep (SWS) and delta power in NREMS in rats and humans, possibly promoting sleep consolidation. The lack of highly selective compounds has limited the interpretation and application of these data. In this study, the ability of four novel 5-HT2a inverse agonists to promote sleep consolidation was measured and compared to zolpidem.
Methods: Male Wistar rats (300 ± 25 g) were housed in a temperature-controlled room under a 12/12 light/dark cycle and were provided food and water ad libitum. Animals (n=8) were anesthetized and instrumented for standard polygraphic recordings (EEG and EMG). Each test compound was dissolved in 80% v/v Tween 80 solution and administered via oral gavage following light sedation (60% CO2/40% O2) approximately 6 hours after lights on. In a repeated measures design, each rat received seven separate doses, with each dose separated by a minimum of 3 days. The first and seventh doses were vehicle and the second through sixth doses were test compounds [AR228295 (1 mg/kg), AR230421 (1.4 mg/kg), AR231135 (1.4 mg/kg), AR231142 (1.4 mg/kg), and zolpidem (5 mg/kg)] given in a randomized counter-balanced order. EEG and EMG data were scored visually in 10s epochs for Waking, REMS and NREMS. Time spent in each state per half-hour was assessed and sleep bout length and number of bouts were calculated for each state in hourly bins as well as EEG delta power (0.5-3.5 Hz). A one-side paired t-test was employed to compare the average change in each parameter from vehicle during a given time interval for each test compound.
Results: Although duration of the effect varied with each test compound, delta power was significantly increased (p<0.05) initially after dosing for all test compounds as compared to vehicle. There was a trend, and statistical significance was reached at some time intervals, for all compounds to increase NREMS bout length, while the number of Waking bouts and NREMS bouts were decreased as compared to vehicle. No significant effects were observed on Waking bout length, REMS bout length and bout number, or total time spent in each state.
Conclusion: These results demonstrate that 5-HT2a inverse agonists promote sleep consolidation in rats during a time in their circadian sleep cycle that their sleep is naturally fragmented. This conclusion is supported by the trend for all compounds to increase NREMS bout length while NREMS and the number of Waking bouts decreased. Delta power during NREMS increased during the same period when sleep consolidation was facilitated, suggesting that these compounds may be promoting deeper sleep as well as sleep consolidation. 5-HT2a inverse agonists may prove to be effective treatments for sleep disorders where sleep

consolidation is desired. More studies are needed to further characterize the sleep effects for this class of compounds.

030

Electrophysiological Effects of GABAB Agonists on Hypocretin/EGFP Neurons in Mouse Hypothalamic Slices

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Introduction: The hypocretin (Hcrt)/orexin system is now recognized as a central neurotransmitter system in the maintenance of wakefulness. Defects in this system, either presynaptically or postsynaptically, result in narcolepsy both in humans and animals. Hcrt neurons receive excitatory glutamatergic and inhibitory GABAergic inputs. Previous studies have shown that GABA inhibits activity of Hcrt cells via GABAA receptors. Recently, it has been shown that GABAB receptor mRNA is present in Hcrt neurons. Here, we report the effects of GABAB agonists on defined Hcrt neurons, which may provide insight into the role of GABAB receptors in sleep regulation.
Methods: Transgenic mice (3-6 weeks of age), in which enhanced green fluorescent protein (EGFP) was linked to the Hcrt promoter (Hcrt/EGFP), were studied. Brain slices (250um) containing the lateral hypothalamus were prepared using a microtome. The slices were perfused with physiological solution containing (mM): NaCl 135, KCl 5, CaCl2 1, MgCl2 1, NaHCO3 25, glucose 10, bubbled with 95% O2, 5% CO2. Hcrt/EGFP neurons were visualized using both infrared and fluorescence microscopy. Whole-cell patch recordings were made using an Axopatch 1D amplifier at room temperature. The internal solution contained (mM): KCl 145, MgCl2 1, EGTA-Na3 1.1, HEPES 10, Na2ATP 2, Na2GTP 0.5, pH 7.2. Drug applications were by bath perfusion at 2ml/min flow rate.
Results: Under control conditions, all Hcrt/EGFP neurons recorded (n = 18) displayed spontaneous firing of action potentials (0.5-3 Hz) superimposed on spontaneous synaptic activity. Most spike overshoots were greater than 40mV though the resting potentials were relatively less negative (approximately -50mV). Tetrodotoxin (TTX, 1 uM) blocked spiking and depressed synaptic activity, indicating that the spikes were generated by the activation of TTX-sensitive voltage-gated sodium channels and the activity was principally driven by neurotransmission. Bath application of the selective GABAB agonist (-)-baclofen (10 - 100 mM) and the GABA metabolite gamma-hydroxybutyric acid (GHB, 1-30mM) caused membrane hyperpolarization and decreases in input residence and membrane excitability. The amplitude of individual action potentials was reduced despite membrane hyperpolarization. Moreover, the frequency of spontaneous action potentials and synaptic activity were also decreased. These drug actions were partially reversible following prolonged washout of the compounds.
Conclusion: These results demonstrate that there are functional GABAB receptors in Hcrt/EGFP neurons. The baclofen and GHB-induced responses in Hcrt neurons are consistent with responses in other types of neurons, for example, hippocampal pyramidal cells. These data suggest that GABA can act on both GABAA and GABAB receptors. Exogenous GHB at high concentrations selectively activates GABAB receptors and produces a profound inhibitory effect on the wake-promoting Hcrt neurons. The cellular action of GHB may underlie its in vivo effect of promoting slow wave sleep and may contribute to its efficacy in the treatment of narcolepsy.

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REM Sleep-Suppressing Effect of Hypothalamic Perifornical Microperfusion with GABAA Receptor Antagonist, Bicuculline, Increases with the Duration of Sleep

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Introduction: Manipulations of GABAergic transmission in the hypothalamic perifornical (PF) region have profound effects on sleep-wake behavior. Last year, we reported that mRNA levels for α-1, α-2 and β-2 subunits of the GABAA receptor increase in the PF region during the afternoon when compared to the morning (Volgin & Kubin, APSS Abstracts, 2003). The goal of the present study was to assess whether these transcriptional changes can be related to circadian time-dependent, endogenous GABAergic inhibitory effects on sleep exerted in the PF region.
Methods: In seven chronically instrumented (cortical and hippocampal EEG, nuchal EMG) rats, the hypothalamic PF region was unilaterally microperfused with the GABAA receptor antagonist, bicuculline (BIC; 20 μM). Sleep-wake and motor activity were recorded for 4 hrs of continuous perfusion with artificial cerebrospinal fluid (CSF) or with BIC substituting for CSF during the middle three hours. Recording sessions with CSF or CSF-BIC-CSF were made in a random order from either 9:00 AM to 1:00 PM (AM sessions) or 12:01 PM to 4:00 PM (PM sessions).
Results: As expected, the amounts of both slow-wave sleep (SWS) and rapid eye movement sleep (REMS) were significantly higher during the PM sessions. The average percentages of SWS and REMS during perfusion with CFS were 41.8±5.2 (SE) and 11.0±2.6 at 10-12 AM. At 1-3 PM, they were 51.8±5.7 ($p<0.009$ re. the AM sessions) and 17.3±2.2 ($p<0.02$ re. the AM sessions), respectively. The most striking finding was that, during the PM sessions, BIC nearly eliminated the afternoon increase in REMS, whereas its effect on SWS was not significant. The average percentages of SWS and REMS during perfusion with BIC were 26.1±4.8 ($p<0.007$ re. CSF-AM) and 4.0±1.8 ($p<0.04$ re. CSF-AM) at 10-12 AM. At 1-3 PM, they were 31.5±10.4 (not different from CSF-PM) and 5.8±1.7 ($p<0.008$ re. CSF-PM), respectively. The effects of BIC on REMS were not correlated with its effects on motor activity; BIC increased the total number of movements during wakefulness in the AM sessions from 768±100/hr to 1500±300/hr ($p<0.04$), whereas its motor effects in the PM sessions were not significant.
Conclusion: The results suggest that the magnitude of GABAergic inhibition increases in the PF region with the duration of sleep, and that this process may be responsible for the characteristic increase in the relative amount of REMS in the second half of the sleep period. The time-dependence of the effect of BIC on REMS may be related to the previously reported afternoon increases of mRNA levels for selected GABAA receptor subunits in the PF region.

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Dorsomedial Pontine Neurons with Axonal Projections to the Medullary Reticular Formation Express Orexin-1 and Adrenergic Alpha-2A Receptor mRNA

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Introduction: Rapid eye movement (REM) sleep can be elicited or suppressed by microinjections of various agonists and antagonists into a discrete region of the dorsomedial pontine reticular formation. However, little is known about the neurons located in this pontine REM sleep-triggering region other than that many have axonal projections to the medial medullary reticular formation. To better understand the modulatory influences that may converge on pontine reticular neurons involved in the generation of REM sleep, we began to investigate the mRNA species that these cells express using single-cell reverse transcription (RT) and polymerase chain reaction (PCR).
Methods: Under pentobarbital anesthesia, fluorescein (FITC)-labeled latex microspheres (100-120 nl) were microinjected into the medial medullary reticular formation of 25-32 day-old rats. After 6 days, the rats were sacrificed under deep isoflurane anesthesia and 1-2 coronal 400 μm slices were obtained from the level of the caudal inferior colliculus. Following enzymatic digestion with papain, 400 μm micropunches were cut out from the dorsomedial pontine reticular formation, cells were mechanically dissociated and plated. Individual cells with FITC-labeled beads were identified, collected and their intracellular contents subjected to DNA digestion followed by RT and semi-nested, two stage PCR.
Results: To date, 25 out of 42 cells tested (59%) were positive for orexin-1 receptor mRNA, 9 out of 22 (41%) for the adrenergic α-2A receptor mRNA, and 4 out of 22 were positive for both.
Conclusion: It was reported that microinjections into the dorsomedial pontine tegmentum of orexin and the α-2 adrenergic receptor antagonist, clonidine, respectively promote and suppress REM sleep. Our results show that dorsomedial pontine neurons with axonal projections to the medial medulla may express appropriate receptors to be postsynaptically affected by these REM sleep-modulating compounds.

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Brain Stem Projections To The Orexinergic Area Of The Posterior/Lateral Hypothalamus

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Introduction: The orexinergic system of the posterior/lateral hypothalamus is involved in the control of sleep-wake status, motor and autonomic activities. Degeneration of orexin neurons is linked to human narcolepsy. Narcoleptic patients also have low level of orexin in the cerebrospinal fluid (CSF). In contrast, orexin level in the CSF was higher in patients with the restless legs syndrome (RLS) than in normal subjects. Our previous study showed that a 6-hydroxydopamine (6-OHDA) lesion, which specifically damages dopaminergic neurons, in the ventral mesopontine junction (VMPJ) including the retrorubral nucleus (RRN) in the midbrain produces insomnia and muscle twitches during slow wave sleep in the behaving cat. The sleep pattern and muscle twitches during sleep seen in the 6-OHDA-VMPJ lesioned cat resemble those of RLS and periodic leg movement disorder patients. We suggest that dopaminergic projections from the VMPJ to the posterior/lateral hypothalamus may be involved in the regulation of orexinergic neuronal activity, which in turn plays a role in the regulation of sleep and motor activity. In the present study, we used retrograde transport tracing combined with immunohistochemical technique to determine areas of the brainstem that project to the orexin neuron area.
Methods: The experiment was performed in 4 rats. WGA-HRP (2.5%/30 nl) was microinjected into the orexin neuron area. Two days after WGA-HRP injection, rats were perfused intracardially with cold saline followed with cold 4% paraformaldehyde solution. The brain tissue was removed and kept in 4% paraformaldehyde solution for 2 hours at 4° C. Then, the brain tissue was stored in 30% sucrose solution. Serial coronal sections were cut at 40 u. Alternate brain sections were stained for tyrosine hydroxylase (TH)/WGA-HRP and choline acetyltransferase (ChAT)/WGA-HRP to identify catecholaminergic and cholinergic projections, respectively. All primary antibodies were purchased from Chemicon.
Results: A very strong projection was found in the superior colliculus and substantia nigra pars reticulata (SNR). A strong projection was found in the medial and lateral parabrachial nuclei, Kolliker-Fuse nucleus, dorsal raphe (DR), central gray, and laterodorsal tegmental nucleus (LDT). A moderate projection was found in the RRN and rostromedial mesencephalic reticular formation, locus coeruleus (LC) and the dorsal division of the principal trigeminal sensory nucleus. A few WGA-HRP labelled neurons were found in the pedunculopontine tegmental nucleus (PPT), pontine inhibitory area, A7 group, nucleus of solitary tract, and the dorsolateral portion of the caudal division of the spinal trigeminal nucleus. WGA-HRP and TH double labelling immunohistochemistry revealed that dopaminergic neurons in the SNR, RRN and DR, as well as noradrenergic neurons in the LC and A7 project to the orexinergic area. Cholinergic projections were found in the LDT and PPT.
Conclusion: Our present finding that dopaminergic neurons in the VMPJ project to the orexinergic area suggest that neurons in the VMPJ may exert an inhibitory effect on orexin neurons. Thus, disinhibition of orexin neuronal activity resulting from dopaminergic neuron hypofunction in the VMPJ may cause insomnia and muscle hyperactivity during sleep.

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034

Stimulation of GABAA Receptors Decreases GAD-67 and GABAA Receptor Subunit mRNA Expression in the Hypothalamic Perifornical Region In Vitro

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Introduction: Extracellular levels of GABA in the hypothalamic perifornical (PF) region are maximal during slow-wave sleep (SWS) (Nitz & Siegel, 1996), whereas antagonism of endogenous GABAA receptor-mediated inhibition in this region suppresses sleep (Kubin et al., Soc. for Neurosci. Abstracts, 2002). The magnitude of this antagonistic effect depends on the circadian time and duration of prior sleep (Lu et al., this meeting), and the same factors alter the expression of GABAA receptor subunit mRNAs in the PF region (Volgin & Kubin, APSS Abstracts, 2003). Together, these data show that GABAergic inhibition in the PF region affects the amount and time course of sleep, and suggest that its magnitude is regulated in relation to sleep amount and timing. To determine whether GABAA receptor-mediated inhibition exerted in the posterior hypothalamus, such as that occurring during SWS, may lead to transcriptional changes, we assessed the effect of exposure of hypothalamic slices in vitro to the GABAA receptor agonist, muscimol, on the expression of genes potentially important for sleep regulation.
Methods: Adult rats were deeply anesthetized with isoflurane and 400 m thick coronal hypothalamic slices were obtained from levels just cau-

dal to the decussation of the optic tract. The slices were divided into two halves along the midline and each half was initially stabilized at room temperature in oxygenated HEPES buffer (pH 7.4, osmolarity 300 mOsm, K+ 5 mM). Then, one half-slice was superfused with control buffer and the other with buffer containing 10 μM muscimol, both for 1 hr at 34-35oC. Additional experiments were performed with synaptic transmission blocked with tetrodotoxin (TTX, 1 μM). Subsequently, two 400 μm micropunches were cut from each half-slice, one from just dorsal to the fornix (PF region) and the other from the adjacent dorsomedial/paraventricular area (DM region). RNA was extracted from each sample, reverse-transcribed and cDNA amplified using quantitative polymerase chain reaction with primers for distinct GABAA receptor subunits, glutamatic acid decarboxylase-67 (GAD-67), GAD-65, preproorexin (PPO), and tubulin as a reference. The amounts of each cDNA in each sample were determined using external standards and then normalized by the amount of tubulin. All measurements were replicated in 4-6 experiments.

Results: In the absence of TTX, muscimol reduced about two-fold the mRNA levels for GAD-67 and α1 and β3 subunits of GABAA receptor, and about five-fold the level of PPO mRNA in the PF samples. The mRNA levels for α2, α3, β1 and β2 GABAA receptor subunits and GAD-65 were not significantly altered. None of these nine mRNAs was significantly affected in the DM region. Increases following muscimol also occurred; the level of signal transducer and activator of transcription-1 mRNA increased in both PF and DM region. In the presence of TTX, most of the effects of muscimol were abolished, but the declines of PPO and β3 subunit of GABAA receptor mRNA levels were still significant.

Conclusion: These results show that the magnitude of inhibition mediated by GABAA receptors decreases in the PF regions when cell activity is suppressed, or directly in response to stimulation of GABAA receptors. The process involves a downregulation of both GABA synthesis and certain GABAA receptors. If present in vivo, these changes could reduce sleep intensity, thereby facilitating restoration of wakefulness.

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035

Effects Of Microdialysis Of Adenosine A1 And A2A Agonists Into Lateral Preoptic Area On Sleep-Wake And Brain Temperature Of Rats

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Introduction: Adenosine is hypothesized to be involved in the homeostatic regulation of sleep. Adenosine exerts its effects through inhibitory A1 and excitatory A2A receptors. A1 receptor activation in basal forebrain induces sleep, possibly by inhibiting wake active neurons. A2A receptor activation in the sub-arachnoid space near the rostral basal forebrain also results in sleep. Since studies of physiological actions of adenosine A1 and A2A receptors in preoptic area - a major sleep promoting center- were limited, we examined sleep, waking and brain temperature after microdialysing CPA and CGS21680 HCl (agonists of A1 and A2A receptors respectively) into the lateral preoptic area (lPOA) of freely moving rats.

Methods: Five male Sprague - Dawley rats were implanted with EEG and EMG electrodes, a thermocouple, and a guide cannula for microdialysis probe into lPOA (AP = -0.4 mm; DV =8.8 mm; L = 1.3 mm from Bregma). A week after surgery, microdialysis probes were inserted and rats were connected to the recording set up. Recordings were started at the beginning of lights-off, 18 hrs after probe insertion. Rats were perfused with ACSF for one hr, followed by two hrs of perfusion with drug (either 25μM CPA or 50 μM CGS 21680 HCl) or ACSF as control. The post-perfusion recording lasted for 20hrs. Each rat was perfused with ACSF and the two drugs, with the sequence of perfusion randomized across rats. Sleep-wake was scored into 5 stages (AW, QW, S1, S2 and REM). Significant differences between control and experimental groups were determined with a one way ANOVA.

Results: CGS21680 HCl perfusion significantly ($p \leq 0.05$) decreased AW (CGS: 15.5 ± 1.3 %) compared to ACSF control (26.5 ± 5.13 %). QW, S1, S2 and REM were not significantly altered from the baseline levels during perfusion. However, 2hrs after the end of CGS perfusion, compared to the baseline, there were significant ($p \leq 0.05$) increases in S1 (CSF: 14.9 ± 1.4%; CGS: 22.22 ± 2.6%) and S2 (CSF: 29.03 ± 2.63%; CGS: 47.33 ± 4.3%), while AW remained lower (CSF: 34.39 ± 5.0%; CGS: 8.81 ± 3.1%). CGS did not affect brain temperature. During CPA perfusion, AW was significantly ($p \leq 0.05$) increased (CSF: 26.5 ± 5.1%; CPA: 61.7 ± 6.1%), and there was a decrease in S1 (CSF: 18.8 ± 3.3 %; CPA: 10.4 ± 2.2 %) and S2 (CSF: 32.4 ± 3.4 %; CPA: 8.5 ± 3.7 %). CPA did not affect QW and REM. CPA transiently (at 40 and 60 mins) but significantly increased temperature (by 1 ° C from baseline) during perfusion.

Conclusion: In lPOA, an A2A receptor agonist suppressed AW and increased both S1 and S2. Sleep induction observed could be due to the excitatory action of CGS21680HCl on sleep active neurons of the lPOA. The delayed onset of a sleep promoting effect of CGS21680HCl suggests that A2A receptors of lPOA may be secondarily involved in sleep and body temperature regulation. Perfusion of an A1 agonist increased AW and decreased S1 and S2. Since CPA is inhibitory, these effects could be due to inhibition of sleep active neurons in the lPOA.

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036

Retrograde Labeling in the Preoptic Area of the Hypothalamus Following Injections of Fluoro-Gold into Perifornical Lateral Hypothalamus

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Introduction: The preoptic/anterior hypothalamus (POAH) is an important sleep regulatory region and also has reproduction, body fluid balance, thermoregulation and neuroendocrine functions. The rostral and caudal parts of the median preoptic nucleus (MnPN) as well as the ventrolateral preoptic area (VLPO) express c-fos protein immunoreactivity (IR) following sustained sleep and nearly 50% of neurons recorded in the MnPN exhibit elevated discharge rates during both nonREM and REM sleep compared to waking. We have shown that sleep-related fos-IR in MnPN neurons co-localizes with the inhibitory neurotransmitter, GABA. Using anterograde tracer, we observed projections from MnPN to arousal systems including serotonergic dorsal raphe area (DR) and noradrenergic locus coeruleus area (LC) and hypocretin IR-neurons in the perifornical lateral hypothalamic area (PFLH). In the present study, retrograde tracer Fluoro-Gold (FG) was injected to PFLH to confirm the MnPN-PFLH projection. Visualization of FG was combined with immunostaining for Glutamate Decarboxylase (GAD), a marker of GABAergic neurons.

Methods: Fourteen male Sprague-Dawley rats (280-320g) received unilateral pressure micro-injections of FG (2% in NaCl; 0.2 ul Volume) aimed at PFLH. Following a 10 day survival period, animals were sacrificed. Sections (40μm in thickness) through the PFLH and preoptic area

were collected and processed for fluorescent visualization for FG or duel visualization for FG with GAD. FG was visualized by auto fluorescent or with Rhodamine Red (RRX) and GAD was visualized with FITC.
Results: Six rats received small FG injections confined to the PFLH area, in the region of hypocretin neurons. In all those rats, numerous FG-positive neurons were observed in the rostral and caudal MnPN. Retrograde labeling was also seen in the lateral preoptic area (LPO), the horizontal limb of the diagonal bands of Broca (hDBB) and the magnocellular preoptic area (MCP). Few retrograde labeled cells were observed in VLPO core area, but some labeled cells were observed in extended VLPO region. More than 50% of the FG-postive neurons in the MnPN were double labeled for GAD. GABAergic projections to the PFLH were not confined to the MnPN. Some of the FG-positive neurons seen in hDBB, LPO also were double labeled for GAD.
Conclusion: Findings with retrograde tracers confirmed our previous finding with anterograde tracer, that MnPN neurons are a source of afferents to the hypocretin neuronal fields in PFLH. Most projection neurons are GABAergic. These findings support the hypothesis that MnPN neurons are a potential source of sleep-related inhibitory modulation of hypocretin arousal systems.

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037

The Noradrenergic System in Sleep and Wakefulness-I: Regulation of Brain Gene Expression

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Introduction: We have recently shown that ~5% of the transcripts in the cerebral cortex change their expression because of sleep and wakefulness independent of time of day. Wakefulness-related transcripts included transcription factors, heat shock proteins, genes related to glutamatergic transmission, and genes involved in synaptic potentiation and the acquisition of new memories. Sleep-related transcripts included glial genes, genes involved in protein synthesis, cholesterol synthesis, membrane trafficking, and genes related to synaptic down-regulation and memory consolidation. Locus Coeruleus (LC) neurons are active during attentive wakefulness and less active during sleep. We had previously shown that the high expression during wakefulness of several genes involved in synaptic plasticity is dependent on an intact LC. It was not known, however, whether norepinephrine (NE) can affect the expression of other state-dependent transcripts. Therefore, we measured transcript levels of thousands of genes in the cerebral cortex of normal rats and in rats whose cortical noradrenergic fibers had been destroyed by pretreatment with the neurotoxin DSP4.
Methods: Male WKY rats pretreated with saline or DSP4 were implanted 1 week later for chronic polygraphic recordings, recorded continuously for 1-2 weeks, and sacrificed after 6 hours of forced wakefulness. Microarrays analysis (Affymetrix RGU34A) was performed on pooled RNA from 7 saline-treated and 7 DSP4-treated rats. Results were confirmed with quantitative PCR on RNA from the same animals and from independent groups of rats (6 saline-treated, 6 DSP4-treated). Cortical levels of NE, dopamine (DA), and serotonin (5-HT) were measured with HPLC.
Results: Cortical NE levels were almost completely depleted by DSP4, 5-HT content was slightly reduced, and DA levels were preserved (mean +/-SEM, DSP4-treated rats as % of controls): NE = 15 +/-3.3%; 5-HT = 73 +/-14%; DA = 104+/-24%. Daily percentages of sleep and wakefulness 2-3 weeks after DSP4 treatment were similar in the 2 groups: wakefulness (controls and DSP4 rats, respectively) = 60.7 +/-1.4, 60.8 +/-1.7; NREM sleep = 30.1 +/-1.2, 30.0 +/-1.4; REM sleep = 8.3 +/-0.7, 9.8 +/-1.4. Out of 4978 genes expressed in the cerebral cortex, >200 (known genes and ESTs) showed reduced expression after DSP4 treatment, while only a few transcripts were expressed at higher levels in LC-lesioned animals. Among the genes whose expression was positively modulated by wakefulness and NE were the previously identified c-fos, NGFI-A, Arc, BDNF, other genes implicated in synaptic plasticity (homer/Vesl, Narp, CDC42, CD24) and several chaperones/heat shock proteins involved in cellular stress responses.
Conclusion: NE modulates the expression of ~4% of cortical transcripts. A small group of NE-dependent transcripts are also modulated by behavioral state; in most cases they are wakefulness-related transcripts. The largest group of genes that are both NE-dependent and wakefulness-related is involved in synaptic potentiation. We have suggested that synaptic potentiation occurring during wakefulness is responsible for the homeostatic increase in slow wave activity during subsequent sleep (Tononi and Cirelli, 2003). Thus, DSP4-treated rats should show a decrease in slow wave homeostasis. This prediction is tested in a companion abstract.

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038

The Noradrenergic System in Sleep and Wakefulness-II: Regulation of Slow Wave Homeostasis

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Introduction: Noradrenergic neurons in the locus coerulues (LC) are active during wakefulness and reduce their firing during sleep. Norepinephrine (NE) released from LC cells enhances information transmission, promotes attentive processes, and enables synaptic potentiation. We previously showed that destruction of noradrenergic fibers with the neurotoxin DSP4 did not affect amount and distribution of wakefulness and sleep. DSP4-treated rats also showed a normal waking EEG dominated by low voltage fast activity. However, in these rats the waking-related induction of genes involved in synaptic potentiation was severely reduced (see companion abstract). We have hypothesized that synaptic potentiation during wakefulness is responsible for the homeostatic increase in slow wave activity (SWA, 0.75-4.5 Hz) during subsequent sleep (Tononi and Cirelli, 2003). This hypothesis predicts that slow wave homeostasis should be reduced in DSP4-treated animals. To test this prediction, we compared slow wave homeostasis in DSP4-treated animals and in saline-treated controls.
Methods: Male WKY rats pretreated with saline (n=21) or DSP4 (n=16) were implanted 1 week later for polygraphic recordings and recorded for 1-2 weeks (LD 12:12). Sleep stages were scored visually and power spectra were calculated for consecutive 4-s epochs (FFT, Hanning window, occipital derivation). Cortical levels of NE, dopamine (DA), and serotonin (5-HT) were measured with HPLC.
Results: Cortical NE levels were significantly reduced in DSP4-treated rats, while 5-HT and DA levels were preserved (mean ?SEM, DSP4-treated rats as % of controls): NE = 17.7+/-5; 5-HT = 87+/-8; DA = 83+/-20. Daily percentages of sleep and wakefulness 2-3 weeks after treatment were similar in the 2 groups (controls: wakefulness 55.1+/-1, NREM sleep 33.9+/-1, REM sleep 11.1+/-1; DSP4-rats: 57.9+/-1, 31.6+/-1, 10.6+/-0.4). Episode number and duration were also similar between the 2 groups. However, the 2 groups differed with respect to SWA homeostasis, which was dampened in DSP4-treated animals: 1) The exponential decrease of SWA during day sleep after a night of wakefulness was reduced in DSP4-treated animals by 40.6+/-12.3% relative to controls ($p<0.05$, unpaired t-test); 2) The increase of SWA after spontaneous waking episodes was absent in DSP-4 treated animals (during sleep following waking episodes >10 min, controls had a 11.7+/-6%

increase in SWA compared to their average SWA for the corresponding 2-h interval; in DSP4-treated rats the change was -4.0+/-3%; group difference was significant at p<0.05, unpaired t-test); 3) The increase of SWA during sleep following 6-h of sleep deprivation was reduced in DSP4-treated animals (the % increase over 24-h baseline values was 192.3+/-10.3 in controls and 145.9+/-22.4 in DSP4-treated rats, p=0.06, unpaired t-test, n=5 animals/group). Preliminary data show that the dampening of SWA homeostasis in DSP4-treated animals persisted under DD conditions.
Conclusion: Lesions of the noradrenergic system do not affect sleep amount and distribution but dampen the SWA homeostatic response. Since noradrenergic lesions prevent the induction of genes related to synaptic potentiation, these results support the hypothesis that synaptic potentiation and SWA homeostasis may be linked.

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A Lateral Pontine Tegmental Flip-Flop Switch For Regulation Of REM Sleep

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Introduction: The pontine tegmentum has been shown to contain both REM promoting and REM inhibitory areas in the past, but the full extent and relationship of these two sites has remained controversial. We examined the descending projections from orexin neurons and from the ventrolateral preoptic nucleus (VLPO), a hypothalamic cell group that promotes both REM and NREM sleep to this region. We found that there are two major regions that receive VLPO and orexin afferents: 1.) The lateral pontine tegmentum (LPT) consists of the lateral periaqueductal gray matter and the lateral parts of the rostral pontine reticular formation. Previous evidence suggests that neurons in these areas may inhibit REM sleep. 2.) The medial pontine tegmentum consists of the cholinergic LDT and PPT cell groups and the non-cholinergic sublaterodorsal (SLD) region, just ventral to the LDT and medial to the PPT. Neurons in these areas fire during REM sleep and are thought to be REM promoting. Neurons in the lateral pontine tegmentum generally express OX2 orexin receptors, whereas neurons in the medial tegmentum express primarily OX1 receptors.
Methods: 1.) Injecting ibotenic acid into the LPT in rats bilaterally and examining sleep change across one day two weeks after the surgery. 2.) Injecting muscimol into the LPT in freely moving rats and examing their sleep behavior 3.) Injecting anterorade tracers into the LPT and retrograde tracers into the perifornical region, the intralaminar thalamus and the spinal cord.
Results: Ibotenic acid lesions of the lateral pontine tegmentum increased the amount of REM sleep by 50-100% across 24 hrs, with the most prominent increases during the night; total NREM was not affected. Acute injections of muscimol into the LPT caused REM-like behavior (atonia, theta range EEG). Injections of anterograde and retrograde tracers into the LPT showed that it mainly targets the perifornical region and zona incerta in the lateral hypothalamus, the intralaminar thalamic nuclei, the medial mesopontine tegmentum, the ventromedial medullary reticular formation, and the spinal cord.
Conclusion: We propose that the lateral mesopontine tegmentum may activate both ascending and descending circuitry that opposes REM sleep, and that the lateral and medial mesopontine tegmentum may inhibit one another, forming a flip-flop switch for REM sleep regulation. This relationship, and the distribution of OX1 and OX2 orexin receptors in the two areas may explain why deletion of the OX2 receptor results in narcolepsy with cataplexy.

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040

The Effects of Basal Ganglia Lesions On Rat Sleep

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Introduction: The basal ganglia (BG) has historically been associated with governing motor function and voluntary reaction, not sleep. However, two previous studies have suggested the possibility that there could be a relation between the functions of the BG and sleep. Corsi-Cabrera et al. (1974) reported a significant increase in paradoxcial sleep (PS) with caudate nucleus lesioning. In contrast, Mena-Segovia (2002) found no significant increase in PS after caudate lesioning, but instead found an increase in waking (W) at the expense of high voltage (HV) sleep. Since the BG is rich in neurotransmitters that promote sleep (e.g. GABA and adenosine), we sought to discern the effects of BG lesioned animals on W and the stages of sleep in rats.
Methods: Five male Sprague-Dawley rats (3 experimental and 2 age-matched controls) were used in this study. The three experimental rats experienced unilateral (left hemisphere) ibotenic acid lesioning of the globus pallidus (GP), while the data for the normal, control rats were from previously scored data in our laboratory. We recorded W and sleep from stereotaxically implanted electrocorticographic, epidural electrodes and frontalis muscle electromyograms according to standard procedures. We recorded during the 12-hour light phase of the 12:12 light-dark cycle. Following recording, histological verification of the lesioned GP sites was done. Data were statistically analyzed using the Mann-Whitney U test.
Results: The results demonstated that GP lesioned rats experienced a statistically significant increase in W (27.3%) compared to normal rats (U = -3.86, p = .000). In addition, lesioned animals exhibited a significant decrease (26.85%) in the amound of HV sleep compared to normal controls (U = -4.397, p = .000). There were no significant differences in the amount of PS between the groups.
Conclusion: This study suggests that the BG may play a significant role in sleep. In particular, these data suggest that the BG may be integral to the regulation of sleep and may help to explain sleep disturbances characterisitic of clinical sleep disorders such as Parkinson's Disease

041

Novel Site Of Action For Nicotine In The Pedunculopontine (PPN) Nucleus

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Introduction: Rapid eye movement (REM) sleep decreases between 10 and 30 days postnatally in the rat with the greatest decrease occurring between 12-21 days. The PPN is known to modulate waking and REM sleep. Patients with schizophrenia, a developmental disorder, manifest increased arousal and REM sleep drive, have more than a 50% incidence in smoking, and are heavier smokers than the general population. We hypothesize that nicotine (NIC) induces an initial inhibitory effect on arousal via receptors in the PPN, thus eliciting a calming effect in these patients. We therefore tested the effects of application of a non-desensitizing NIC agonist and a NIC antagonist on developing PPN neurons.
Methods: We recorded intracellularly from PPN neurons in 12-21 day rat brainstem slices maintained in artificial CSF. The a-4 nicotinic receptor agonist dimethylphenylpiperazinium (DMPP, 50uM) was applied using a picospritzer . The a-4 nicotinic receptor antagonist mecamylamine (MEC, 10uM) was superfused through the bath for one minute,

as was tetrodotoxin (TTX, 0.3uM).
Results: We analyzed 25 PPN type II cells shown previously to be 2/3 cholinergic. 24/25 cells tested responded to DMPP and all responses were blocked by MEC, showing that the responses were presumably due to an a-4 nicotinic receptor. The mean /-SE hyperpolarization was 4 /-0.9mV (n=5) and depolarization was 5.1 /-0.4mV (n=19) with an average duration response of one minute. When tested after TTX superfusion, DMPP did not elicit an effect in the cells that initially depolarized, showing that this was an indirect response. However, the cells that initially hyperpolarized showed the same response following TTX, demonstrating that it was a direct response of a-4 nicotinic receptors on these PPN cells.
Conclusion: The NIC agonist DMPP produced an inhibitory response on 20% of the type II PPN cells tested. These findings suggest that NIC, by acting directly on some PPN neurons, has the capacity to produce a calming or anxiolytic effect. Therefore, smoking may serve as a form of self-medication for patients with disorders such as schizophrenia that include hypervigilance and increased REM sleep drive due to overactive PPN output.

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A Novel Procedure for Sleep Deprivation and Sleep Fragmentation in Rodents

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Introduction: Sleep Deprivation (SD) and Sleep Fragmentation (SF) are common clinical conditions for which the morbid consequences are yet to be fully defined. While several models of SD in rodents are currently available, none of them adheres to the animal life conditions, potentially interfering with the evaluation of the pathophysiological consequences of SD. Furthermore, no appropriate model has been validated to allow for the study of SF and SD using similar sleep disruption strategies. To address these issues, we developed a novel experimental procedure that allows for both SD and SF in rodents.
Methods: Adult male C57BL6 mice were exposed to acute or to chronic SD and SF. The procedure was based on a novel device adapted to the regular cage, automatically and silently disturbing the animals 8 h per day in a continuous mode for SD or every 2 min for SF. Up to 10 animals were placed in the cage one day prior to the procedure for acclimation, with access to food and water ad libitum. Animals were tested acutely or chronically (up to 10 days) then sacrificed for blood sampling. In addition, acute SD with the new device was compared to SD using the classical platform procedure.
Results: Following overnight acclimation, the animals behaved as in their regular cage without any device. During the SD procedure, the animals were gently and continuously maintained awake (total+/-SD) while during the SF procedure, the animals were briefly and intermittently awaken every 2 min, immediately falling back asleep closely grouped together. Weight evaluation before and after the 8 h procedure showed a discrete variation between the 3 groups in terms of percentage of weight loss (controls = 1.98 +/-0.54 %; SF = 3.84 +/- 1.01 %; SD = 4.77 +/- 0.60 %, n = 10 for each group, p=0.047, Kruskal-Wallis test), independently of food intake (weight variations in fasted animals during the same procedure: controls = 4.42 +/- 1.29 %; SF = 6.48 +/- 1.07 %; SD = 7.41 +/- 0.97 %, n = 10 for each group, p=0.0003, Kruskal-Wallis test). In contrast, more prominent differences in weight were observed in animals exposed to SD with the platform procedure (13.2 +/- 1.91 %, n = 4).
Conclusion: We have developed a novel procedure that permits application of both SD and SF in rodents. Compared to other existing procedures, our novel approach closely mimics usual life conditions (housing, social group interactions, physical activity, noise, humidity, access to food and water), as demonstrated by overall behavioral patterns and weight evolution. Therefore, this experimental model should allow for more reproducible and accurate testing of the cognitive and metabolic consequences of SF and SD in rodents, thereby minimizing procedure-related artifacts. The biological markers and sleep architecture characterization of this model are currently in progress.

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Cholinergic and Dopaminergic Neurotransmission in the Rat Dorsal Striatum is Required During the PSW for Radial Maze Learning

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Introduction: It has been proposed that REM sleep is involved in the consolidation of many tasks during intervals termed Paradoxical Sleep Windows (PSW). For the radial arm maze (RAM), the PSW occurs 0 - 4 hr following training. Both REM deprivation during the PSW and electrolytic lesions to the rat dorsal striatum, result in poor performance on the RAM, indicative of impairments in consolidation of the task. The hypothesis tested here is that cholinergic neurons (normally active during REM) and dopaminergic neurons (critical for learning) within the dorsal striatum are both required during the PSW for the RAM for effective consolidation of the task.
Methods: Experiment One: Rats (N=148) were randomly assigned to groups that received systemic injections of scopolamine (0 - 0.4 mg/kg, 0 and 2 hr after training; 0.006 mg/kg, 4 and 6 hr after training), cis-flupenthixol (0 - 1.0 mg/kg, 0 hr after training; 0.25 mg/kg, 8 hr after training) or trans-flupenthixol (0.25 mg/kg, 0 hr after training) on each of 9 successive days after RAM training. RAM training had food-deprived rats placed into an 8-arm maze that had the same 4 arms baited day-to-day. Animals explored the maze until all 4 baits were consumed or 6 min had passed, whichever came first. Response latencies and numbers of total arm visits were recorded. Experiment Two: Rats (N=141) had bilateral guide cannulae inserted into their dorsal striata and were randomly assigned to groups that received intrastriatal infusions of scopolamine (0-18 mg/mL/side 0 and 2 hr after training; 18 mg/mL/side 4 and 6 hr after training), cis-flupenthixol (0-25 mg/mL/side 0-4 hr after training; 6 mg/mL/side 4 or 12 hr after training), or trans-flupenthixol (6 mg/mL/side 0 hr after training) following training on the RAM (as above).
Results: Data were analysed using survival analyses and mixed design analysis of variance (ANOVA). Results showed that with timing consistent with the PSW for the RAM task, groups of animals receiving systemic or intrastriatal scopolamine were impaired relative to controls; however, the effect was not seen in groups given the drug outside of the PSW. Similarly, groups of animals receiving systemic or intrastriatal cis-flupenthixol during the PSW were also impaired in the acquisition of the RAM; however, the inactive trans isomer showed an effect when given systemically but not intrastriatally. Further, the dopamine receptor blocker had an effect on consolidation when given 4 and 12 hr after training.
Conclusion: Our results indicate that cholinergic neurons, specifically within the dorsal striatum are required to be active during the PSW for effective consolidation of the RAM. Our central infusion study suggests

that dopaminergic neurotransmission within the dorsal striatum is also required for acquisition of the RAM; however, dopaminergic neurons are required to be active beyond the PSW for the RAM task.

044

Sleep Is Increased In Mice With Obesity Induced By High Fat Food

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Introduction: Obesity is a major health problem in modern societies. Obese subjects display excessive daytime sleepiness (EDS). Although EDS has been well documented in obese humans, obesity-associated sleep alterations have not been characterized in animals except in two studies using Zucker rat, which is a genetic obesity model. Since increased food intake, particularly high fat food, is a major factor in the development of obesity, we determined sleep alterations in during the developmental course of obesity induced by high fat food.
Methods: Adult male C57BL/6 mice (6 month of age) were implanted with electroencephalogram (EEG) and electromyography (EMG) electrodes. Animals were kept on a 12:12 h light-dark cycle. After 2 weeks of recovery from the surgery and 4 days of adaptation to the recording procedure, baseline EEG and EMG were continuously recorded for 24 h, and further for 24 h in the 2nd, 4th, 6th, and 10th weeks. After baseline EEG and EMG recording, mice were fed on high fat food (Bio-Serv, Frenchtown, NJ; product number F3282, n=11), or on regular high protein food (Harlan Tekled, Madison, WC; Product No. 2018; n=10). Sleep was scored visually.
Results: 1. In the high fat group, the body weights were steadily and significantly increased during the 10-week period. The body weight was significantly increased from 30.7+/-0.4 gm at baseline to 35.4 gm at 2nd week ($t(19)=2.82$, $p<0.01$) and reached to 45.0+/-1.8 gm by the 10th week ($t(19)=5.93$, $p<0.0001$). The control animals did not show significant change in body weight (31.3+/-0.6 gm at baseline and 32.2+/-1.2 gm at the 10th week). 2. In the high fat group, non-rapid eye movement sleep (NREMS) was significantly increased ($F(4,40)=7.411$, $p<0.0001$) at 2nd (+14.85+/-0.60%, $p<0.05$), 4th (-15.10+/-0.33%, $p<0.05$), 6th (-19.20+/-0.76%, $p<0.05$) and 10th (+11.40+/-0.51%, $p<0.05$) weeks compared to the baseline. Wakefulness (W) was significantly decreased ($F(4,40)=7.718$, $p<0.0001$) at 2nd (-13.25+/-0.79%, $p<0.05$), 4th (-13.65+/-0.44%, $p<0.05$), 6th (-16.62+/-0.93%, $p<0.05$) and 10th (-8.67+/-0.72%, $p<0.05$) compared to the baseline. The alterations of NREMS and W were not dependent on the time of day. Rapid eye movement sleep (REMS) was not significantly altered from the baseline. 3. In the control group, NREMS was not significantly altered from the baseline except in the 10th week (+8.59+/-1.28%, $p<0.05$). Wakefulness was slightly reduced at the 10th week compared to the baseline (-9.60+/-1.27%, $p<0.05$). 4. The changes of sleep compared to the baseline were significantly different between the control and high fat groups at 4th ($F(1,10)=5.874$, $p<0.04$) and 6th ($F(1,10)=7.191$, $p<0.03$) weeks.
Conclusion: The present results indicate that NREMS is increased and W is reduced in an animal model of obesity. These observations are consistent with human studies that obesity is associated with EDS.

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045

Amphetamine Mediated Release of Dopamine is Markedly Enhanced in Juveniles Exposed to Intermittent Hypoxia as Neonates

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Introduction: Intermittent hypoxic insults, occurring during a period of critical brain development, lead to persistent reductions in dopaminergic signaling evident in juveniles and young adults. Within the striatum, extracellular levels of dopamine are significantly diminished while vesicular monoamine transporter (VMAT2) and dopamine D1 receptors are markedly elevated (Decker 2002). These observations led us to hypothesize that dopamine may be presynaptically sequestered in post-hypoxic rats, attributing to reduced dopaminergic tone in mesostriatal circuitry.
Methods: Six male Charles River Sprague-Dawley rats were studied. Following birth, pups were undisturbed and maintained by the dam. On post natal (PN) day 7 pups were randomly assigned to either an intermittent hypoxia-inducing chamber (n=3), or a normoxic chamber (n=3). Between PN 7-11, pups in the hypoxia chamber received 6 hours of intermittent hypoxia per day while pups in the normoxia chamber were exposed to bursts of room air. At the conclusion of the protocol on PN 11, all pups were permitted to mature without further intervention, until weaning at PN 21. Microdialysis: On PN day 40, a guide cannula was surgically implanted inserted into the striatum. Following two days of surgical recovery, rats were placed in a Plexiglas box for a 24 hour adaptation period. Then, the guide cannula was removed and a microdialysis probe inserted. Following baseline data collection, at 6:00 PM, 3.2 mg/kg of d-amphetamine was injected interperitoneally and microdialysis samples were collected at thirty minute intervals during the subsequent six hours. Following a 36 hour recovery, the same protocol was repeated, except that d-amphetamine was injected at 10:00 AM. The sequence of injections (6:00 PM vs 10:00 AM) was randomized between rats. Dialysate samples were assayed for dopamine concentration using high performance liquid chromatography electrochemical detection with a reversed phase column.
Results: D-amphetamine significantly increased extracellular dopamine (mean percent change from baseline ± SEM) in the striata of both post-hypoxic and control rats. Injections immediately preceding the major wake period (viz. 6:00 PM) induced a 2,693% ± 570% increase in post-hypoxic rats compared with an 88% ± 38% increase in control rats ($p < 0.001$). Injections during the major sleep period (viz. 10:00 AM) increased extracellular dopamine to the same amount in post-hypoxic and control rats (153% ± 45% vs 127% ± 31%, $p = 0.642$). With regards to post-hypoxic rats, the dopaminergic response to d-amphetamine challenge was markedly augmented at 6:00 PM vs 10:00 AM.
Conclusion: We demonstrate enhanced dopaminergic responsiveness to d-amphetamine in juvenile rats exposed to intermittent hypoxic insults between PN days 7-11. In addition, we observed a circadian modulation of the dopaminergic response to amphetamine in the post-hypoxic rat. These data are consistent with our hypothesis that neonatally occurring hypoxic insults promote sequestering of dopamine within presynaptic terminals, leading to reduced dopaminergic tone within mesostriatal circuitry. The mechanisms underlying dopamine sequestering and the circadian gated response to amphetamine are currently being investigated.

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046

Developmental Changes Of Ih And Ia In Pedunculopontine (PPN) Neurons

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Introduction: Rapid eye movement (REM) sleep decreases between 10 and 30 days postnatally in the rat with the majority occurring between 12 and 21 days. The PPN is known to modulate waking and REM sleep, therefore, it is important to understand at a cellular level what may be causing this decrease, and possibly uncover novel areas for the dysregulation of the PPN that is seen in disorders such as schizophrenia, which manifest increased arousal and REM sleep drive. Ih is a hyperpolarization activated nonselective cation current that serves to drive the cell membrane to a less polarized level. Ia is a current that when activated acts to slow the return to firing levels following hyperpolarization.
Methods: We recorded intracellularly from PPN neurons in 12-21 day rat brainstem slices maintained in artificial CSF. We identified cholinergic vs non-cholinergic PPN neurons using intracellular injection of biocytin processed for Texas Red-avidin immunocytochemistry and NADPH diaphorase histochemistry. PPN neurons were identified based on intrinsic membrane properties, type I (LTS), type II (A) and type III (A LTS), as previously described. Measurements were taken following 300msec hyperpolarizing pulses of 0.1-0.9nA in bridge mode. The 1/2max Ia duration and 1/2max Ih amplitude were calculated across age. A one-way ANOVA was used for statistical analysis.
Results: Type II cholinergic PPN neurons aged 12-16 and 17-21 days expressing only Ia showed a mean /-SE of 51.6 /-11.2 msec and 94.7 /-17.1 msec, respectively ($n=18$, $F=4.4$, $p<0.05$). Ih amplitudes for day 12-16 and 17-21 cells were 1.6 /-.4 mV and 2.75 /-.4 mV, respectively ($n=14$, $F=31.7$, $p<0.0001$). When Ia duration was analyzed in cells expressing both Ia and Ih compared to those with only Ia at all ages the mean /-SE was 39.5 /-4.0 msec vs 87.4 /-16.6 msec ($n=20$, $F=7.6$, $p<0.01$).
Conclusion: During the developmental decrease in REM sleep, the duration of Ia significantly increased, suggesting that this current is working to slow the firing frequency of those type II cholinergic PPN cells with Ia. During the same period, the amplitude of Ih increased significantly, suggesting that it is acting to increase firing and minimize the effect of IPSPs. Cells that expressed both Ih and Ia had significantly shorter duration Ia currents (when compared to those with only Ia), suggesting that this subset of PPN cells tends to fire faster. Overall, these findings describe significant changes in intrinsic membrane properties in PPN neurons during the developmental decrease in REM sleep.

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047

Novel Site Of Action For Nicotine: Inhibition Of Pedunculopontine (PPN) Output, Blockade By Mecamylamine

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Introduction: The vertex-recorded midlatency auditory P50 potential in humans is thought to be generated, at least in part, by the reticular activating system (RAS). The rodent P13 potential is analogous to the human P50 potential. In both species, this potential is a) sleep state-dependent (present during waking and paradoxical, but not slow-wave, sleep), b) habituates at low frequencies of stimulation, and c) blocked by the muscarinic antagonist scopolamine (cholinergic PPN neurons may help generate the P50 and P13 potentials). Decreased amplitude of the P50 potential is present in narcolepsy, while decreased habituation is evident in such psychiatric disorders as schizophrenia, depression and posttraumatic stress disorder (PTSD). Excessive smoking is a hallmark of patients with these psychiatric disorders. This study determined the effects of systemically administered nicotine (NIC) on the manifestation of the P13 potential in the rat, and if its effect could be blocked by the a-4 nicotinic antagonist mecamylamine (MEC) injected into the PPN.
Methods: Adult male rats (n=8) were implanted with transcranial screws at the vertex 1 mm lateral to the midline bilaterally and a reference screw in the frontal sinus, and wired to a plug cemented to the skull. Alert rats received pairs of stimuli (2 clicks, 0.1 msec duration each at 1kHz, 103 dB, 500 msec inter-pair interval) presented 5 sec apart in a sound-attenuating chamber. Evoked potentials were digitized and averaged (32 trials) every 10 min up to 1 hr after an injection of 0.6 mg/kg NIC s.c., compared to saline injection, and to NIC s.c. after pre-treatment with 10, 30 or 100 nmol MEC injected locally into the PPN
Results: We previously reported that the amplitude of the vertex-recorded P13 potential induced by the first stimulus of a pair (initial responsiveness) was reduced in a dose-dependent manner by NIC. The NIC concentration used (0.6 mg/kg) induced a statistically significant decrease in P13 potential amplitude for 20 min post-injection. However, pre-treatment with 30 and 100 nmol MEC blocked this reduction, while 10 nmol MEC had no effect on the NIC-induced reduction of P13 potential amplitude.
Conclusion: These results show that the P13 potential, a manifestation of PPN outputs to the thalamus related to arousal state, is 1) reduced by NIC s.c. injection at doses similar to those in heavy smokers, 2) the inhibitory effect on the P13 potential is blocked in a dose-dependent manner by injection into the PPN of the a-4 nicotinic antagonist MEC. These findings suggest that the NIC from smoking may induce an initial inhibitory effect on PPN neurons, thus reducing arousal and producing a calming or anxiolytic effect. Smoking may, therefore, be a form of self-medication for patients with disorders that include hypervigilance such as schizophrenia, depression and PTSD.

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048

Distribution of c-Fos Protein Immunoreactivity in the Median Preoptic Nucleus During Sleep Versus Hyperosmotic Challenge

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Introduction: Recent work from our laboratory has identified the median preoptic nucleus (MnPN) of the hypothalamus as a potential sleep-regulatory site. MnPN neurons exhibit immunoreactivity (IR) for c-Fos protein following sustained sleep, but not following sustained waking. Sleep-related Fos-IR is predominately localized in MnPN GABAergic neurons. A majority of neurons recorded in the MnPN of unanesthetized rats display elevated discharge rates during both nonREM and REM sleep compared to waking. The MnPN has previously been implicated in the regulation of body fluid balance. Treatments that activate thirst, such as systemic injections of hypertonic saline or intracerebroventricular administration of angiotensin also activate c-Fos protein IR in MnPN neurons. The present study was undertaken to determine if the pattern of Fos-IR occurring during sleep is similar to or different from the pattern evoked by systemic administration of hypertonic saline.
Methods: Subjects were adult male Sprague Dawley rats (280-320 g) maintained on a 12/12 light/dark cycle (lights on at 06:00). Rats were surgically prepared with chronic cortical screw electrodes and neck EMG electrodes to electrographically record sleep-waking states. Following surgery, rats were well-adapted to a recording chamber and recording cables. On the experimental day, rats were given an injection

of either hypertonic saline (HS; 1.5 M, 1cc/100g body weight, IP) or normal saline (NS; 1cc/100g body weight, IP) at 09:00. EEG and EMG activity were continuously recorded for the next 90 minutes. Rats were not permitted access to drinking water during the recording period. At 10:30, rats were deeply anesthetized with Nembutal followed by cardiac perfusion with 1) phosphate buffered saline and 2) 3% paraformaldehyde. Following equilibration with 30% sucrose, 40µ frozen sections through the hypothalamus were cut. Sections were double immunostained for c-Fos protein and glutamic acid decarboxylase (GAD), a marker of GABAergic neurons.

Results: All rats treated with HS exhibited intense Fos-IR bilaterally in the supraoptic nucleus, while no Fos-IR was present in this nucleus in NS-treated rats. HS treated rats exhibited moderate numbers of Fos-IR neurons in the caudal portion of the MnPN, both dorsal and ventral to the anterior commissure. Fewer Fos-IR neurons were observed in the rostral portions of the MnPN. In all portions of the MnPN examined, Fos-IR in HS treated rats was predominately located in neurons that were not immunoreactive for GAD. NS-treated rats that did not sleep during the 90 min recording period had a near complete absence of Fos-IR throughout the rostral to caudal extent of the MnPN. Sleeping rats exhibited Fos-IR that was predominately located in MnPN neurons that were also immunoreactive for GAD. Fos-IR neurons were more numerous in the rostral and caudal MnPN in sleeping versus HS-treated rats.

Conclusion: These preliminary results indicate that different populations of MnPN neurons are activated in response to sleep and osmotic stimuli.

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049

Increased Activity Reduces Cataplexy in Canine Narcolepsy: Possible Role of Elevated Hypocretin Level

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Introduction: Loss of hypocretin (Hcrt, orexin) neurons (Thannickal et al., 2000) and reduced levels of hypocretin (Peyron et al., 2000) cause most human narcolepsy. Mutations of the genes responsible for the synthesis of hypocretin and its receptors have also been shown to cause narcolepsy. The most thoroughly investigated such mutant is the Hcrtr2 mutant narcoleptic dog. We found that intravenous administration of Hcrt reduces cataplexy in these animals (John et al., 2000). Our work also showed that extended periods of increased locomotor activity lead to a significant increase in central Hcrt-1 levels, as measured in cerebrospinal fluid in these dogs (Wu et al., 2002). We therefore hypothesized that increased locomotor activity would decrease cataplexy.

Methods: We used fifteen genetically narcoleptic (Hcrtr2 mutant) Doberman pinschers. Dogs (n=15) were kept active (increased locomotor activity/exercise) in an outdoor exercise area for 15, 30, 60, 120 min or kept awake in a room for the 120 min as a control. A modified Food Elicited Cataplexy (mFECT) test was performed between 5-10 min after the termination of the exercise period. To study the time course, the FECT was done (n=11) before the exercise, 5-min., 15 min., 30 min., 60 min. and 120 min. after termination of exercise. In a separate study, a high dose of the D1/D2 receptor agonist apomorphine (4mg/kg i.v.) was given (n=6) to induce cataplexy and Hcrt-1 level was measured. In all studies CSF was collected from the cisterna magna under thiopentol anesthesia. Hcrt-1 was extracted from 0.5-1 ml samples with a reversed phase SEP-PAK C18 column. An iodine-125 Hcrt-1 radioimmunoassay was used to measure concentration in reconstituted aliquots (Wu et al., 2002).

Results: The level of cataplexy was significantly ($P<0.01$ for all, Bonferroni t-test) reduced after 15 (61.8±22.3 sec), 30 (43.0±15.1 sec), 60 (49.7±18.3 sec) or 120 (28.6±11.4 sec) min of exercise relative to alert waking (150.5±22.7 sec). FECT showed that cataplexy level remained low for an hour in all exercise groups (15, 60, 120 min). The severity of cataplexy returned to the pre-exercise level after 60 min in the 15-min exercise group whereas it remained reduced for 2hrs in 60 and 120 min exercise group. Increased activity for 60 and 120 min produced a large increase in Hcrt level that remained elevated for 2hrs after the termination of exercise. We also found that apomorphine significantly reduced Hcrt-1 ($p<0.05$, Bonferroni t-test) and produced extended periods of cataplexy lasting 30 or more minutes.

Conclusion: This study shows that Hcrt release is correlated with the duration of increased motor activity. We found that elevated levels of Hcrt-1 resulting from increased activity are correlated with reduced cataplexy. Since the Hcrtr2 is mutated in these dogs, Hcrt must be acting through Hcrt-1 receptors or other unidentified receptors to reduce cataplexy. In summary, Hcrt level is inversely correlated with cataplexy occurrence in Hcrtr2 mutant animals.

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050

Regional Cerebral Metabolic Correlates of Electroencephalographic Activity During Stage-2 and Slow Wave Sleep: An H215O PET Study

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Introduction: Electroencephalographic (EEG) studies suggest that characteristic patterns of neural activity serve functional roles in the initiation and maintenance of sleep. Recent research has used MEG dipole localization to identify the brain regions and structures associated with these sleep-related neural patterns, but the spatial resolution of such techniques remains limited. To clarify the neural basis of these electroencephalographic events, we correlated cerebral metabolic activity using H215O Positron Emission Tomography (PET) with the frequency of sleep spindles, k-complexes, and percent delta sleep during stage-2 and slow wave sleep (SWS).

Methods: Nine (9) healthy male subjects were scanned during wakefulness and during sleep using a Scanditronix PC2048-15B tomograph. Upon identification of a sleep stage, data were acquired in 15 (6.5mm) planes simultaneously, parallel to the cantho-meatal line following injection of a bolus of 30 mCi of H215O. Data were acquired as 16 frames over a 4-minute period while subjects were continuously monitored polysomnographically. EEG data were scored independently for frequency of sleep spindles, k-complexes, and percentage of delta activity during the scanning period. PET data were analyzed using statistical parametric mapping (SPM99). Scans were realigned and normalized into stereotaxic space and smoothed with a non-isotropic Gaussian filter of 10x10x6mm full width at half maximum [FWHM]. Random effects models were used to examine the correlation between cerebral metabolism and EEG variables during Stage-2 and SWS. Statistical Parametric Maps were set to a height threshold of $p < .001$ (uncorrected), with an extent (k) threshold of 10 contiguous voxels. Metabolic activity data were then extracted for 59 predefined regions using the Automated Anatomical Labeling Atlas and Masks for Region of Interest Analysis software programs. Mean intensity values for each region were then subjected to a discriminant function analysis to identify those regions that most reliably discriminated between Stage-2 and SWS.

Results: Stage-2 Sleep: Spindle frequency positively correlated with metabolic activity in the right anterior cingulate gyrus, and reduced activity in the left thalamus and left superior temporal gyrus. K-complex frequency positively correlated with activity in the left orbitofrontal cortex, left thalamus, bilateral anterior cingulate, bilateral temporal cortex, and right insula and cerebellum, while negatively correlating with activity in the left middle temporal gyrus. Slow Wave Sleep: Delta percentage positively correlated with bilateral insular activity, right frontal and temporal cortex, and left hippocampus activity, while correlating negatively with left orbital frontal activation. Discriminant Function Analysis: Of the regions analyzed, metabolic activity within the left thalamus and right hippocampus significantly discriminated the two sleep states, correctly classifying 83% of cases, ÷2=9.95, $p < .007$.
Conclusion: The frequency of spindles and k-complexes during Stage 2 sleep and the percentage of delta activity during SWS were each associated with distinct patterns of metabolic activity within cortical and subcortical regions. Sleep stages were accurately classified based on the magnitude of metabolic activity within the left thalamus and right hippocampus. The correlative findings are consistent with the putative role of sleep spindles and k-complexes in initiating and maintaining sleep.

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Interaction Between The Corticotropin-Releasing-Factor System And Hypocretins: Components Mediating The Stress Response

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Introduction: The hypocretins (orexins) are two recently described peptides that have been shown to play a crucial role in behavioral arousal. Several lines of evidence suggest that hypocretins (Hcrts) could constitute a key relay for mediating stress behavior. Hcrts interact with autonomic, neuroendocrine and neuroregulatory systems. Centrally administered Hcrt-1 activates the hypothalamo-pituitary-adrenal (HPA) axis, induces plasma corticosterone, and glucocorticoids modulate Hcrt mRNA expression. Moreover, central administration of the alpha-helical corticotropin-releasing factor (CRF) antagonist blocks Hcrt-induced grooming behavior. Finally, restraint stress has been shown to induce an up-regulation of pre-prohypocretin mRNA. In this study, we tested the hypothesis that activation of the Hcrt system is a critical component of the stress response activated by CRF. To address this issue, we 1) determined the anatomical interactions between CRF and Hcrt systems, 2) assessed ex vivo CRF effects on orexin/EGFP neurons in hypothalamic slices, and 3) assessed whether the stress-induced activation of Hcrt neurons occurs through CRF receptor 1 (CRF-R1).
Methods: 1) We conducted double labeling immunohistochemical experiments with an antibody directed against pre-prohypocretin (#2123;1:1500) in combination with antisera against CRF (Santa Cruz Inc; 1:500) or CRF-R1 receptors (Santa Cruz Inc,1:1000) in control animals. 2) Hypothalamic slices were obtained from orexin/EGFP mice and, after visualization and identification of Hcrt neurons, CRF (100 nM, 300 nM) was applied by bath application and membrane potential was recorded by patch clamp electrophysiology. 3) CRF-R1 knockout mice (provided by Dr Wylie Vale) and their control littermates were subjected to mild foot shock or 30 min restraint stress. Activation of Hcrt neurons was assessed by double-labeling using Fos protein as the marker of neuronal activation.
Results: 1) A dense network of projections connecting CRF and Hcrt neurons was detected in the lateral hypothalamus. We also observed synaptic boutons from Hcrt neurons connecting CRF perikarya in the paraventricular hypothalamic nuclei and the central nucleus of the amygdala. In addition, Hcrt neurons were found to express the CRF-R1 receptor. 2) Application of 100 nM or 300 nM CRF caused depolarization of membrane potential and increased firing rate in a subpopulation of 32 orexin/EGFP neurons. The response to CRF was concentration-dependent. 3) We observed an attenuation of the induction of Fos in Hcrt neurons of CRF-R1 knockout mice subjected to footshock or restraint stress.
Conclusion: We have shown anatomical and physiological links between the peptidergic CRF and Hcrt systems. Our data suggest that CRF-R1 may mediate the stress-induced activation of Hcrt system.

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Modeling Wakefulness and Sleep in a Large-scale Thalamocortical Model

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Introduction: During non-REM sleep, virtually all cortical neurons undergo slow oscillations in their membrane potential that are synchronized by thalamocortical circuits and reflected in EEG slow waves. These oscillations have been investigated in vivo, in vitro and in isolated cortical slab preparations using intracellular, extracellular and EEG techniques. To help identify intrinsic and network mechanisms responsible for generating, maintaining and terminating these oscillations, we have constructed a large-scale computer model that incorporates detailed cellular properties as well as the main features of the anatomical organization of thalamocortical circuits.
Methods: We constructed a large-scale model of the cat thalamocortical system (~65,000 neurons and 6 million connections) capable of producing rich spontaneous activity as well as orientation-selective responses to visual stimuli during wakefulness. The model encompasses two visual areas divided into three layers (supragranular, infragranular and layer IV) with the associated thalamic and reticular thalamic nuclei. Model neurons (excitatory and inhibitory) are highly interconnected with patterned thalamocortical, corticothalamic, and intra- and interareal corticocortical connections. The model also incorporates experimentally observed intrinsic currents that are thought to affect sleep rhythms, including: a hyperpolarization-activated depolarizing cation current IH; a depolarizing Ca2+ current IT; a hyperpolarizing background leak K+ current IK; a hyperpolarizing Na+ activated potassium current IK(Na); and a depolarizing persistent sodium current INa(P). Intrinsically bursting (IB) neurons in the thalamus were modeled by adding IT and IH, while IB cells in layer V contained IH and INa(P) currents. The leak current IK was increased (sleep) or decreased (wakefulness) to mimic the action of neuromodulatory systems. The SYNTHESIS simulator was used to model the network.
Results: In the waking mode, the model exhibited highly variable spontaneous activity throughout the cortex as well as orientation selective responses to visual stimuli. Evoked visual activity displayed gamma frequency thalamocortical synchronization. In the sleep mode, the model displayed spontaneously occurring slow oscillations that resembled those observed in vivo and in vitro. A systematic investigation, using computer simulations, of the effects of intrinsic currents and network parameters on the initiation, maintenance and termination of the slow oscillation leads to the following generalizatons: 1. An increase in potassium leak conductance is sufficient to trigger the transition from wakefulness to sleep. 2. The combination of INa(P) and IH in layer V IB cells and INa(P) in all cortical cells is sufficient to initiate the up-state of the

slow oscillation. 3. The combination of intrinsic (INa(P)) and synaptic (AMPA and NMDA) currents is sufficient to maintain the up-state. 4. Sodium-activated potassium (IK(Na)) is sufficient to terminate the up-state. 5. Synaptic depression modulates the duration and synchronization of the slow oscillation. 6. Corticocortical projections in the model synchronize the slow oscillation, consistent with findings from physiological experiments.
Conclusion: We have constructed a large-scale model of the visual thalamocortical system that combines intrinsic cellular properties with the main features of thalamocortical anatomy and replicates key aspects of neural activity in wakefulness and sleep. Simulations using this model suggest mechanisms for the initiation, maintenance and termination of the up- and down-states of the slow oscillation of sleep.

053

A Critical Role for NADPH Oxidase in Long-Term Intermittent Hypoxia-Induced Hypersomnolence

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Introduction: Over 8 million adult Americans have obstructive sleep apnea syndrome, and a large number of people who present with sleep apnea and hypersomnolence will continue to manifest significant daytime sleepiness, despite effective therapy (Patel et al., 2003; Weaver et al., 2003). Our recent studies show that long-term (>=6 wks) intermittent hypoxia (LTIH) in mice, modeling the hypoxia/reoxygenation patterns of sleep apnea, results in large increases in 24hr sleep time and increased sleepiness following short-term sleep loss (Veasey et al., 2004). This LTIH-induced hypersomnolence is associated with markers of significant oxidative injury (including tyrosine nitration, protein carbonylation and lipid peroxidation) in many brain regions, including wake-promoting regions. A major source of superoxide radical in the brain is microglial NADPH oxidase. We hypothesized that LTIH, as in sleep apnea, activates microglial NADPH oxidase and that this is a major source of superoxide anion resulting in oxidative injury to wake-promoting neurons. To determine the role NADPH oxidase plays in LTIH hypersomnolence, we measured microglial activation and induction of NADPH oxidase in mice exposed to sham LTIH or LTIH and then characterized the effects of LTIH on sleep in mice lacking functional NADPH oxidase activity.
Methods: Adult male C57BL/6J mice were exposed to LTIH (n=8) or sham LTIH (n=8) 10 hrs of the lights-on period per day for 8 weeks. Following a two week recovery in normoxia, mice were euthanized, perfused in sterile saline and brains were cryocut (10um) coronal slices for laser-capture microdissection in wake- and sleep-promoting nuclei (100 20um dia captures per sample). Real-time PCR (primer/taqman probes) were use to quantify transcrional changes. In a second experiment, mice lacking functional NADPH oxidase activity via transgenic loss of one of the subunits (gp91phox) were implanted for electrophysiological sleep recordings and sleep latency testing (Veasey et al., 2004) after a 2 wk recovery from 8 weeks sham LTIH of LTIH (N=10/group).
Results: Transcriptional results. LTIH resulted in marked increases in NADPH oxidase subunit transcription n wake-promoting and hypoxia sensitive brain regions (100%=500% increases in copy numbers in magnocellular, substantia inominata, nucleus basalis of Meynert, locus coeruleus and dorsal raphe, $p<0.05$), with little change observed in sleep-promoting regions (VLPO, median preoptic). MAC-1, an indicator of microglial activation, is increased in parallel with gp67phox. Other regions with marked increases were hippocampus CA1 and caudat putamen. Effects of LTIH on sleep in gp91phox-/- mice. In contrast to the significant effects of LTIH on wildtype mice (increased NREM (2hr) and REM 24 hr (0.5hr) sleep times, $p<0.05$, null mice were completely resistant to LTIH effects. In addition, sleep latency at baseline and after short term forced wakefulness was also not increased by LTIH in null mice.
Conclusion: Here we show that LTIH results in activation of microglia with upregulation of NADPH oxidase in wake-promoting regions of the basal forebrain and brainstem. Further, mice devoid of NADPH oxidase activity (gp91phox-/-) are fully resistant to both LTIH hypersomnolence and oxidative injury in these brain regions. Finally, inhibition of microglial activation in the basal forebrain largely prevents LTIH hypersomnolence. Thus, NADPH oxidase activation in wake-promoting regions of the brain is essential for the persistent hypersomnolence observed in a model of the hypoxia/reoxygenation events of sleep apnea. This work shows the importance of oxidative injury in LTIH-hypersomnolence and provides a potential therapeutic avenue for the treatment of residual sleepiness in millions of Americans with obstructive sleep apnea.

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Delta EEG Spectral Power during NREM Sleep Positively Correlates with Whole Brain Metabolism across Subjects

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Introduction: To investigate the neurobiological basis of delta EEG spectral power during NREM sleep, we assessed delta (0.5-4 Hz) EEG spectral power and whole brain metabolism during NREM sleep simultaneously in normal healthy participants.
Methods: Healthy participants (ages 30-60 yrs, n=15) completed EEG sleep and [18F]fluoro-2-deoxy-D-glucose positron emission tomography (PET) studies during the first NREM period of a night of sleep. Delta (0.5-4 Hz) EEG spectral power in the 20 minutes period coinciding with maximal radionuclide uptake was computed. Whole brain glucose metabolism during this same time was assessed using an indirect method.
Results: There was a positive correlation (Spearman's rho = .732, p=.003) between whole brain metabolism and delta power during the NREM uptake period across the 15 healthy participants.
Conclusion: The positive correlation between delta power and whole brain metabolism during NREM sleep indicates that, at least across subjects, delta power is directly related to a metabolically active process in the brain. Future studies are now required to determine if these same relationships hold true within a subject as the homeostatic sleep drive is increased via sleep deprivation. If so, this would imply that sleep homeostasis is a metabolically active brain process.

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Effects Of Apnea On Synaptic Efficacy In The Hippocampal CA3/CA1 Pathway In The Cat

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Introduction: Patients with Obstructive Sleep Apnea (OSA) incur deficits in the functioning of the hippocampus and related structures that are involved in the generation of neurocognitive deficits and mood disorders. We hypothesize that the recurrent facilitation of the CA3/CA1 pathway during repetitive episodes of apnea in OSA patients promote

excitotoxic effects that result in the irreversible damage of CA1 neurons. As a first step to test this hypothesis, we examined the effects of apnea on synaptic efficacy within the hippocampal CA3/CA1 pathway in the in vivo cat preparation.

Methods: Experiments were performed on four adult cats. Surgical procedures to expose the dorsal hippocampus were carried out under isoflurane anesthesia. After the completion of all surgical procedures, the animals were anesthetized with α-chloralose (60 mg/kg; i.v.) or urethane (1.6 g/kg, i.v.) and immobilized with flaxedil (1 mg/kg, i.v.). A recording microelectrode filled with 2M NaCl was placed into CA1 and a stimulating metal electrode was positioned into CA3. The level of hemoglobin O2 saturation (SpO2), which was monitored using a pulse oximeter, was maintained constant at 97-99%. Episodes of ventilatory arrest (i.e., apnea; 1 to 1.5 minutes in duration) were conducted to produce a decrease in SpO2 similar to that which occurs in OSA patients (i.e., 50% SpO2). The synaptic efficacy of the CA3/CA1 pathway was examined prior to (control), during, and following apneic episodes using single-pulse, paired-pulse and tetanic stimulation.

Results: Episodes of apnea produced significant changes in the CA1 field potential response (fEPSP) to CA3 stimulation. Typically, a few seconds after the onset of ventilatory arrest (SpO2: 70-80%), the CA1 fEPSP increased in amplitude. Subsequently, the CA1 fEPSP decreased in amplitude until it virtually disappeared at 50% SPO2. The restoration of ventilation promoted the reappearance and recovery of the CA1 fEPSP to its control amplitude. Following a period of approximately two minutes, the CA1 fEPSP response was potentiated by 30-100% compared to that recorded during control conditions. This potentiated state lasted for approximately 10 minutes following the termination of the apneic episode.

Conclusion: The present data confirm and extend the concept that episodes of apnea enhance synaptic efficacy within the CA3/CA1 pathway. Furthermore, our results indicate that the in vivo cat preparation can be employed as a model to investigate synaptic plasticity in the hippocampus induced by chronic, recurrent episodes of apnea. In addition, the present data support our hypothesis that potentiation of CA1 synaptic responses following each episode of apnea in OSA may trigger intracellular mechanisms that are deleterious to the normal functioning of CA1 neurons.

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Locomotor-Dependent And -Independent Regulation Of Hypocretin-1 (Orexin A) In The Squirrel Monkey

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Introduction: Hypocretins are hypothalamic peptides believed to be crucial in the normal functioning of wakefulness. Dysfunction of the hypocretin system leads to the sleep disorder narcolepsy. One of the deficits in narcolepsy is the lack of a normal circadian alertness signal, which helps to consolidate wakefulness into a single daily bout. CSF concentrations of hypocretin-1 have a daily rhythm with a peak late during the wake period of a squirrel monkey, a diurnal South American primate who exhibits consolidated sleep and wake, as do humans. Locomotor activity has been shown to be able to influence hypocretin-1 concentration in dogs, cats, and rodents, though these species are more dependent upon external stimuli for the expression of wakefulness.

Methods: In a group of ten mature female squirrel monkeys (Saimiri sciureus sciureus), we examined the relationship of hypocretin-1 and cortisol with a variety of locomotor conditions and times of day. CSF samples were obtained at 10:00, 13:00, 16:00, and 19:00 under baseline condition and restricted movement conditions. Additional CSF samples were obtained at 10:00 after environmental enrichment and forced locomotor conditions. Hypocretin-1 and cortisol concentrations were determined by commercially available assay.

Results: Activity restriction caused a reduction in locomotion of 82.8 % ± 2.50 %. The activity restriction also caused a significant increase in cortisol (220.7 % ± 64.5 %) at each time tested ($p < 0.05$, paired T-test). Comparison of CSF hypocretin-1 concentrations collected in baseline versus restricted activity conditions, however, indicates no significant difference at any time point ($p > 0.05$, T-test). Examination at of hypocretin-1 concentrations 10:00 under restricted, baseline, enriched, and forced locomotor conditions, though, did reveal a modulatory effect of locomotion. CSF hypocretin-1 concentrations were 19.1 % higher in the enriched activity condition and 39.1 % higher in the forced locomotion condition. There was a significant effect of locomotor condition ($p < 0.01$, ANOVA) and post-hoc analysis indicated a significant difference in CSF hypocretin-1 concentrations between the restricted activity condition and the enriched and forced locomotor conditions, and between the baseline and forced locomotor conditions ($p < 0.05$, Tukey HSD test).

Conclusion: The results of the restricted activity condition indicate that significant locomotor activity is not necessary for the normal diurnal rise of CSF hypocretin-1 to occur. As indicated by the forced and enriched locomotor conditions, however, locomotion elevated over baseline conditions modulates CSF hypocretin-1 concentrations. The relative insensitivity of the squirrel monkey hypocretin-1 system to low locomotor activity may reflect the animal's ability to maintain long, continuous wakefulness in the absence of environmental stimulation - possibly in contrast to polyphasic species such as rodents, dogs, and cats.

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Evidence for Localized Sleep States in Nearby Cortical Columns

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Introduction: In order to understand sleep regulation, many studies are taking a more detailed look at localized EEG during sleep/wake states. Typical sleep studies consider only that the whole animal is asleep or awake. However, if sleep begins at the neuronal group or cortical column level, a variety of its output features may be individually state dependent, independently of whole animal sleep. This study provides a novel way to look at local EEG, and provides a new substrate to interpret the effects of sleep on the temporal patterns of evoked responses in the brain.

Methods: Sprauge-Dawley rats were instrumented for sleep recordings and trained to sleep under restrained conditions by daily gentle handling and restraining. During a typical 2 to 3 hour recording, animals were continuously presented at every 1 to 2 s randomized intervals with 0.2 ms whisker twitches. To compare cortical column state across different whiskers, two whiskers were stimulated at the same time, either on opposite hemispheres for probing interhemisphereic differences, or on the same side for probing ipsilateral differences. We previously identified state specific surface evoked potentials (SEPs) after auditory clicks and whisker twitches. In agreement with previous studies by us and others, SEPs were larger during quiet sleep (QS) over both waking and REM sleep. Individual time triggered responses were also plotted continuously for the whole record to assess the progression of the SEP

changes. For each evoked response, the P1/N1 amplitude difference was measured, registered in time with the 2s scoring bins, and plotted across time after smoothing with a 5 point moving box car algorithm.
Results: Individual SEP amplitudes showed significant periodic fluctuations between high and low amplitudes during the sleep-wake cycle, although the amplitude was usually high during QS and low during waking. Bilateral stimuli produced SEP amplitude fluctuations that usually covaried, but with frequent hemispheric SEP differences, suggesting localized modulation. Two neighboring whiskers twitched simultaneously on the same side produced SEPs that could be mapped using surface electrode arrays. Again, we observed highly correlated fluctuations in the SEP amplitude with frequent divergences, indicating localized modulation between nearby cortical columns. The fraction of time each localized region spent in the low amplitude wake-like state plotted against the subsequent high amplitude sleep-like state showed an average 0.5 correlation with a near unity slope (1.1).
Conclusion: We have established a set of observable parameters that may allow us to assess sleep state of local brain regions based on the characteristics of the evoked responses to sensory stimulation. Since these markers fluctuate independently from whole animal behavioral state, and are frequently different between hemispheres and nearby cortical columns, sleep may be localized to brain regions at least as small as cortical columns. These in-vivo experiments go a long way in demonstrating how the brain could be organized to produce sleep, and provide insights in to the mechanism of local sleep and even of sleep function.

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Sensory Threshold Increases During Active Sleep in Infant Rats
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Introduction: An increase in sensory threshold is a defining feature of sleep in adult animals. This feature, however, has yet to be documented in infants. Here, defining active sleep as the convergence of myoclonic twitching and nuchal muscle atonia, we explore changes in olfactory threshold by exposing infant rats to different concentrations of odorants during sleep and wakefulness.
Methods: Eight-day-old Sprague-Dawley rats were used. In all pups, muscle tone and behavior were monitored to determine behavioral state and respiratory rate was monitored to detect sniffing. Sniffing, or polypnea, indicated that the subjects had detected the stimulus. First, to assess changes in sensory threshold during sleep, in Experiment 1 pups were exposed to 4 concentrations of dimethyl disulfide (DMDS) and a vehicle control. Second, to assess the effect of nutritional state on the pups responses to the odor, in Experiment 2 pups were exposed to 4 concentrations of DMDS at 1-, 5-, or 10-hours post-feeding. Third, to determine whether trigeminal or olfactory inputs were mediating the sniffing response, in Experiment 3 olfactory inputs were eliminated by transecting the lateral olfactory tracts and subjects were exposed to DMDS and glacial acetic acid (GAA; a strong trigeminal stimulus). Finally, to determine whether pups would sniff to a trigeminal stimulus, in Experiment 4 subjects were exposed to several concentrations of GAA while awake or asleep.
Results: Experiment 1 showed that pups were much more likely to sniff to a stimulus when they were awake; in addition, pups were more likely to sniff in response to a higher concentration of DMDS than a lower concentration, especially while asleep. The results clearly indicated that infant rats exhibit an increased olfactory threshold while asleep. Experiment 2 revealed that pups responses to DMDS are modulated by nutritional state; pups responded most strongly to DMDS after a 5-hour deprivation period. In Experiment 3 it was found that the elimination of olfactory inputs resulted in an abolition of sniffing. Finally, in Experiment 4 it was found that pups exposed to a trigeminal stimulus arouse without sniffing. Interestingly, we found evidence that pups often sniff while asleep, that is, polypnea was often observed while pups exhibited myoclonic twitching against a background of muscle atonia.
Conclusion: These results are the first demonstration of an increased olfactory threshold during sleep in infant rats. This finding was selective to the olfactory system as evidenced by elimination of sniffing to DMDS when olfactory input from the bulbs was eliminated. The finding that infant rats often sniff while asleep was unexpected because sniffing has traditionally been viewed as a measure of arousal. Finally, when the present results are coupled with other experiments from our laboratory showing that pain thresholds increase during sleep, it is becoming clear that this defining feature of sleep, increased sensory threshold, is shared by infants and adults.

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In Vitro Electrophysiology of Rat Subcoerulean Neurons
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Introduction: Studies over many years in the cat have implicated a region ventral to the locus coeruleus (subcoeruleus), as being critically involved in the control of rapid-eye-movement (REM) sleep. More recent studies in the rat suggest that the corresponding region in this species also plays an important role in the regulation of this state: 1) Electrolytic lesions of this area abolish the muscle atonia of REM sleep. 2) Injections of the GABAA receptor antagonists bicuculline or GABAzine induce a REM-like state. 3) Neurons in this region project to REM-active, glycine immunoreactive neurons in the ventral medulla. This pathway has been shown to be critical for muscle atonia in the cat. 4) Infusions of carbachol into this region have been shown by Datta and colleagues to trigger P waves. Here we describe the electrophysiological properties of subcoerulean neurons. Furthermore, we have begun to identify the neurotransmitter phenotype of the recorded cells.
Methods: Coronal brainstem slices were prepared from 8-16 day-old rats using a vibratome. Brain slices (150, 200 or 250 microns thick) between -9.16 and -9.8 from bregma rostrocaudally (according to the Atlas of Paxinos and Watson) were cut from each animal and placed in a recording chamber on the stage of an upright microscope (Zeiss Axioscop FS) equipped with a C7500-50 infra-red sensitive digital CCD camera (Hamamatsu), where they were perfused with oxygenated artificial cerebrospinal fluid. Patch electrodes (3-6 MOhm, when filled with a potassium gluconate based intracellular solution) were positioned in the area of the subcoeruleus (subCA, subCD). Neurons were selected for recording using infrared differential interference microscopy (IR-DIC). Whole-cell patch-clamp recordings were performed using an Axopatch 1D or a Multiclamp 700A amplifier (Axon instruments). Neurons were marked during recording by diffusion of 0.5 % Lucifer Yellow in the patch solution. Following electrophysiological recordings the slices were fixed briefly (5 min to 2 hours) in 4 % paraformaldehyde and then stored in phosphate buffer containing 30 % sucrose. Subsequently, in situ hybridization was performed for the mRNA of the vesicular glutamate transporter VGLUT2 to identify glutamatergic neurons.
Results: The neurons could be broadly divided into two groups. Type I neurons (n = 33) were silent at rest and had brief action potentials (2.0 ± 0.1 ms) followed by clearly delineated fast and slow afterhyperpolarizations (AHPs). 18/33 neurons showed a low-threshold spike (LTS) fol-

lowing hyperpolarizing pulses whilst 4/33 neurons showed a delayed return to baseline. Type II neurons (n = 37) were spontaneously active and had broader action potentials (3.5 ± 0.3 ms) followed by a single, continuous AHP. Both type I and type II neurons fired tonically when depolarized by current injections with little or no accommodation of firing. One type I neuron with a prominent LTS was positively identified as being glutamatergic.
Conclusion: The intrinsic membrane properties of subcoerulean neurons closely resemble those of other reticular formation neurons. The ability to correlate the neurotransmitter phenotype of the recorded neurons with their electrophysiology will enable a new depth of understanding of how this important region functions.

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Alterations In Cortical Protein Profiles Across Spontaneous Sleep-Wakefulness

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Introduction: Cholinergic neurotransmission is differentially regulated across spontaneous sleep-wakefulness. Preliminary studies of choline aceytltransferase (ChAT) expression of across spontaneous sleep-wake bouts revealed an apparent inverse relationship between chat mRNA and its protein activity, suggesting that dynamic intracellular changes underlie sleep-wake transitions (Greco et al., 1999). Recent advances in protein separation allow for the identification of total protein signatures that can serve as regional templates to identify specific proteins, metabolic pathways and intracellular mechanisms that underlie sleep-wakefulness. We tested the hypothesis that cortical protein expression varies across spontaneous sleep-wake bouts. We monitored relative protein levels and cellular phosphorylation status by two-dimensional electrophoresis (2D gels) in cingulate cortex using the experimental protocol originally designed to examine chat mRNA.
Methods: Male Sprague- Dawley rats (250- 350g) were implanted with EEG/EMG electrodes and a femoral vein catheter. The rats were housed in a controlled environment (12h lights on/off; lights on 7 am) and recorded continuously for at least 24h prior to sacrifice. All animals were euthanized via pentobarbital injection into the femoral vein between 3-4 pm. Rats were sacrificed under the following conditions: 1) after 10 minutes waking (n=3); 2) following 10 minutes non-REM sleep (n=3); 3) as a function of the time of day, independent of behavioral state (n=2). The cingulate cortex was dissected from coronal sections and immediately frozen. Tissue was homogenized in buffer containing 30 mM Tris (pH8), urea, thiourea, CHAPS, ampholytes (pH 3-10), protease inhibitors, DNAse and RNAse. Proteins were separated by isoelectric focusing (IEF) in the first dimension, followed by molecular mass in the second dimension. SYPRO ruby was used to visualize protein expression patterns. To compare cellular activity across state, the relative phosphorylation state was profiled using a phospho- specific stain (Molecular Probes) and scanned. Data from imaged gels were analyzed using either PDQuest (BioRad) or DeCyder (Amersham Biosciences) 2D analysis software.
Results: The analysis of protein expression and activity profiles is in progress. The results reflect preliminary analysis of a small subset of the proteins profiled at the time of abstract submission. For comparison of relative protein levels, a small subset of proteins (<25,000 daltons, pI 4-7) was analyzed. Qualitatively, no significant change in the number of spots was detected across state. A comparison of patterns across state indicates three 3 relative expression subsets- one that is decreased in SWS relative to waking, a second that is wake-specific and a third that does not change across behavioral state. Most phosphorylated proteins are found in the pI 3-6 range; MW 25- 75 KDa, independent of behavioral state. Qualitatively, the phosphorylation state of cells appears to be diminished during SWS compared to waking. SWS patterns show decreased phospho-specific staining and a decreased number of phospho-reactive spots compared to wake.
Conclusion: These preliminary data suggest that extracellular signaling associated with spontaneous sleep-wakefulness can influence the level and the activity of intracellular proteins, a result consistent with previous reports documenting changes in either specific protein and/or mRNA expression across spontaneous sleep or following sleep deprivation.

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Sleep and Thermoregulation in Rats with Suprachiasmatic Nuclei Lesions

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Introduction: The suprachiasmatic nuclei (SCN) drive the circadian rhythm of body temperature and modulate sleep/wake activity. Body temperature and sleep/wake behavior are also under homeostatic regulation. For example, changes in ambient temperature cause compensatory changes in thermoregulatory behavior so that body temperature is maintained within a narrow range. Sleep and body temperature regulation have a reciprocal relationship, such that changes in body temperature are associated with changes in sleep, and vice versa. This synchrony between body temperature and sleep regulation may partly be a consequence of them both being controlled by a common pacemaker, the SCN. However, there is also an underlying homeostatic interaction between these two behaviors. In the intact rat, any homeostatic regulation of temperature and sleep/wake activity is masked by the over-riding circadian rhythmicity. To examine homeostatic regulation of sleep and body temperature in rats at different ambient temperatures, independently of circadian effects, we therefore eliminated the circadian rhythm by lesioning the SCN.
Methods: Radio-frequency lesions of the SCN were performed under anesthesia in male Sprague-Dawley rats. Rats were also implanted with radio transmitters for monitoring body temperature and locomotor activity, and instrumented for polygraphic and brain temperature recordings. Lesions were deemed successful if a significant periodicity, based on the chi-square periodogram, was absent in 10-day body temperature records of rats kept in constant dim light. Rats with sham lesions (controls) were included in the study for comparison. Sleep and body temperatures were continuously recorded in rats over 24-hours at three different ambient temperatures: moderate (23oC), cold (18oC) and hot (30-31oC).
Results: At a moderate ambient temperature, the control rats showed a circadian rhythm in body temperature, whereas the SCN-lesioned rats (SCNx) had a prominent 4-5 hour ultradian temperature rhythm (amplitude 1-1.5oC) with no circadian rhythm. The two groups of rats had similar 24-hr mean body temperatures in the three ambient temperature conditions, with all rats showing a small increase in body temperature (0.2oC) in the heat, but no change in body temperature in the cold, compared to the moderate condition. SCNx rats, therefore, are able to thermoregulate as efficiently as intact rats, at least when challenged by a mild change in ambient temperature. SCNx rats, however, had a blunted amplitude of their ultradian temperature rhythm in the hot condition compared to moderate and cold conditions. The SCNx rats had the same average amounts of NREM and REM sleep over 24-hours at moderate temperature, compared to controls but sleep bouts were distributed with

an ultradian rhythm of 4-5 hours. The majority of sleep bouts occurred at body temperature troughs and wake coincided with body temperature peaks. Cold disrupted sleep in both groups of animals in a similar way: REM sleep was decreased, especially in the first 12 hours of exposure. At a higher ambient temperature, however, SCNx rats had more REM sleep compared to moderate temperature and to controls, whereas controls tended to have less REM sleep than at moderate temperature.
Conclusion: The SCN modulates the amplitude of ultradian temperature fluctuations and the response of REM sleep to mild ambient warming.

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Conditioned Fear Cues Suppress REM Sleep In Rats

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Introduction: Fear conditioning in rodents has been used to model anxiety disorders in humans. We have reported previously that one session of contextual fear conditioning leads to REM sleep (REMS) suppression when rats are tested 24-h post-conditioning. In mice, fear conditioning to a discrete cue similarly affects REMS. The purpose of the present study was to assess whether analogous changes in sleep architecture occur in rats, and to determine whether cue-induced changes in sleep truly reflect classical conditioning.
Methods: Subjects were male Sprague-Dawley rats (300-350 g). Electrodes for chronic recording of EEG and EMG were implanted. Animals recovered from surgery and were habituated to the recording chamber for 4 h on each of two days. On the following day, baseline sleep was recorded over 4 h (1100 to 1500). One day later, rats in the experimental group (n = 4) received 5 tone-footshock pairings. The tone (90 dB; conditioned stimulus (CS)) remained on for 5 s; the footshock (0.5 mA; unconditioned stimulus, US)) was 1-s in duration and co-terminated with the tone. Stimulus presentations were administered every 3 min, and the conditioning session was approximately 18 min. Conditioning sessions were conducted in a different chamber and room than baseline and post-conditioning recordings. Twenty-four h after conditioning, subjects received 5 CS- alone presentations, and sleep was recorded for 4 h. Control subjects (n = 4) received the same number of tone and footshock presentations, but in a pseudorandom order in which a US could occur at anytime during the training session except during or 30 s following a CS presentation. Twenty-four h later, the controls also received 5 CS-alone presentations prior to their 4-h recording session. Sleep efficiency (sleep time/recording time), and REMS and non-REMS (NREMS) percentages (REMS time/sleep time and NREMS time/sleep time, respectively) were calculated for both groups. Data were analyzed via repeated measures ANOVA.
Results: In the experimental group, exposure to the CS alone strikingly suppressed REMS % (23.9 ± 1.5 vs. 17.2 ± 1.3, $F(1, 8) = 173.57$, $p < 0.001$) but did not affect sleep efficiency (61.3 ± 4.1 vs. 57.2 ± 4.7, $F(1, 8) < 1.0$). In the control group, REMS % did not significantly change (21.5 ± 0.2 vs. 28.2 ± 2.3, $F(1, 8) = 8.6$, $p = 0.06$), nor was sleep efficiency affected (71.8 ± 2.0 vs. 69.7 ± 1.5, $F(1, 8) < 1.0$).
Conclusion: Similarly to mice, rats exposed to a discrete cue previously paired with shock showed REMS suppression. This change in REMS is not simply due to previous shock presentation, as the unpaired control group did not display a decrease in REMS. In fact, this group showed a trend towards an increase in REMS %. The amygdala is a critical modulator of sensory influences on sleep. Many studies have implicated the lateral nucleus of the amygdala (LA) as a key locus of the acquisition and expression of cued fear conditioning. We are currently evaluating the role of the LA in cue-conditioned REMS changes.

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Modulation Of Respiratory Motor Output By Serotonergic Neurons Of The Medullary Raphe Obscurus

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Introduction: Medullary raphe neurons innervate motoneurons of the respiratory pump and pharyngeal muscles, including the diaphragm and genioglossus (GG). Raphe neurons also project to medullary neurons involved in respiratory rhythm generation as well as autonomic neurons modulating blood pressure. Stimulation of raphe neurons increases motor outflow to the diaphragm and GG muscles and increases respiratory rate, with these effects attributed to release of serotonin (5-hydroxytryptamine, 5-HT). However, not all raphe neurons are serotonergic and the specific contribution of serotonergic raphe neurons to the modulation of GG and diaphragm activities in-vivo has not been determined. Furthermore, since a subset of 5-HT raphe neurons are stimulated by hypercapnia these neurons may also contribute to the integrated respiratory responses to CO2 stimulation. This study tests the hypothesis that inhibition of medullary raphe serotonergic neurons will decrease GG and diaphragm muscle activities and respiratory rate, and decrease respiratory responses to hypercapnia.
Methods: Ten urethane-anesthetized, spontaneously breathing, tracheotomized and vagotomized adult rats were studied. Diaphragm and GG muscle activities, blood pressure and the electroencephalogram were recorded. Microdialysis probes were placed into the nucleus raphe obscurus for perfusion of artificial cerebrospinal fluid (ACSF) and 8-OH-DPAT (10μM, 100uμM and 1mM dissolved in ACSF) to inhibit serotonergic raphe neurons. Measurements were performed during room air and CO2-stimulated breathing (7.5% inspired CO2). Microdialysis sites were confirmed by post-mortem histology.
Results: Inhibition of raphe neurons caused dose-dependant decreases in GG and diaphragm activities and blood pressure ($P<0.001$) with statistically significant effects observed at 100μM 8-OH-DPAT ($P<0.05$). At this dose, GG and diaphragm activities decreased by $63.6 \pm 8.5\%$ and $12.9 \pm 3.1\%$ respectively with this observed suppression of GG activity being more than the diaphragm ($P=0.0002$). The magnitude of the significant decline in blood pressure with 100μM 8-OH-DPAT was 12.6 +/- 3.2 mmHg, consistent with a role of serotonergic neurons in blood pressure regulation. In contrast to the significant effects of 8-OH-DPAT on respiratory muscle activities, there was no effect of raphe neuron inhibition on respiratory rate ($P=0.228$) during room air or CO2-stimulated breathing. However, the diaphragm muscle responses to CO2 stimulation was affected by 8-OH-DPAT at the raphe nuclei ($P=0.003$) such that the significant diaphragm responses observed during perfusion of ACSF ($P<0.001$) were abolished with 1mM 8-OH-DPAT ($P=0.104$).
Conclusion: The suppression of GG and diaphragm muscle activities following application of 8-OH-DPAT to the nucleus raphe obscurus is consistent the concept of an endogenous serotonergic drive from raphe neurons to the respiratory system that modulates motor outflow, with this effect being larger for the GG muscle. The abolition of diaphragm muscle responses to CO2-stimulation following inhibition of raphe neurons is also consistent with a role for these serotonergic neurons in contributing to the integrated respiratory motor responses to hypercapnia. Since the activity of serotonergic raphe neurons is known to be increased in wakefulness and decline in sleep, these serotonergic neurons may

constitute a component of the 'wakefulness stimulus' for breathing, a concept that remains to be tested in a freely behaving preparation.

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Gamma Band Oscillation During Rat Whisker Evoked Responses Under Different Anesthetics, Waking and Sleep Conditions

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Introduction: The evoked response potential (ERP) recorded from somatosensory cortex after whisker stimulation is a complex signal containing many frequencies generated by different populations of neurons. State related differences in neuronal firing pattern elicit significant differences in the ERP. By means of filtering the recorded cortical signal, it is possible to obtain an ERP profile across several important frequency bands and identify specific changes under different experimental conditions. Several authors have defined general anesthesia as a behavioral state characterized by loss of consciousness, immobility and lack response to stimulation (eg. Tanelian et al. 1993). We hypothesize that if the Gamma band is a marker of consciousness, then its amplitude should be reduced or absent under unconscious states.
Methods: Anesthetized Sprauge-Dawley rats were recorded using a 25 electrode array (100 um stainless steel wire) placed on the surface of the somatosensory cortex. We performed experiments under Isoflurane (0.5-2.5%), Ketamine (100mg/kg I.M.) / Xylazine (10mg/kg I.M.), Ketamine (100mg/kg I.P.) / Xylazine (10 mg/kg I.P), Urethane (2g/kg I.P.), Propofol (500 mg/kg/min IV), and Pentobarbital (70 mg/kg I.P). We also recorded unanesthetized rats across awake and sleep states under movement restrained conditions. Paradigms of somatosensory random stimulation were carried out while recording local field potentials. We obtained the filtered ERP between 35 to 40 Hz, 200 to 400 Hz and 400 to 600 Hz using both FFT and IIRC techniques.
Results: We found differences in the Gamma frequency band (35-45 Hz) which decreased close to zero amplitude only from rats anesthetized under Isoflurane when comparing with the ERP under Ketamine/Xylazine, Urethane, Propofol, and Pentobarbital. The Gamma burst and the high frequency 200-400 and 400-600 Hz bursts are present during awake, sleep, and all other anesthetic conditions. It is important to point out that our surface field evoked potential recordings conditions have a higher spatial and temporal resolution (100 um and 0.05 ms respectively) than magnetoencephalographic studies. Preliminary results in our laboratory show that ketamine injection reverts the loss of the Gamma band during Isoflurane.
Conclusion: The burst between 35-45 Hz of the ERP might be generated by populations of gabaergic neurons acting within the cortico-thalamic circuit. Others have proposed that consciousness arise from the cortico-thalamic communication through the Gamma band (Llinas R., Ribarry U., 1993), however were not recording field evoked potentials from small neuronal groups as presented here. Since general anesthesia has been defined as a state with loss of consciousness, the results of the current study suggest that consciousness could be generated by other mechanisms as well.

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Abnormalities In Functioning Of Forebrain Neuronal Populations Involved In Sleep-Wake And Circadian Rhythms Regulation In Rats With Genetic Absence Epilepsy

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Introduction: The EEG hallmarks of generalized epilepsy, spike-wave discharges (SWDs) predominantly occur during the states of decreased vigilance. In addition, SWDs show circadian rhythmicity in patients with absence epilepsy and in genetic absence epileptic rats. To test the involvement of sleep-wake controlling and circadian mechanisms in the genesis of absence epilepsy we conducted two series of experiments in rats with genetic absence epilepsy (WAG/Rij strain): 1) a study of neuronal activity within sleep- and waking-promoting structures; 2) a study of c-Fos-immunoreactivity (c-Fos-IR) in forebrain neuronal populations implicated in sleep-waking cycle and circadian rhythms regulation.
Methods: Rats were surgically prepared with EEG and EMG electrodes for sleep-wake state monitoring. Neuronal activity was recorded extracellularly from the median preoptic nucleus (MnPN) and basal forebrain using 20 μm stainless steel microwires. Sleep-related c-Fos-IR was examined in 6 rats during the first half of the light period and compared with data obtained in normal Sprague-Dawley (S-D) rats.
Results: Sleep-active (n=25) and wake-active (n=35) MnPN and basal forebrain neurons showed tonic reciprocal changes in their activity during SWDs that occurred in quiet waking and NREM sleep. All sleep-related units exhibited decreases in firing rate or virtual cessation of firing, whereas wake-related cells increased their discharge. These changes preceded by several seconds, or coincided with the appearance of SWDs. The pattern of sleep-related c-Fos-IR in WAG/Rij rats significantly differed from that in S-D rats. WAG/Rij rats showed an approximately twofold increase in sleep-related c-Fos expression in the MNPN and did not exhibit sleep-related changes in the counts of c-Fos+ cells within ventrolateral preoptic area (VLPO). In rats sleeping 75-80% of time during two hours prior to sacrifice, with a relatively low density of SWDs (15-20 per hour), c-Fos-IR within orexinergic and histaminergic cell groups was close to controls, whereas in animals with a high density of SWDs (30-40 per hour) the percentage of c-Fos+ orexinergic and histaminergic neurons was elevated (15-25%). In animals sleeping less than 50% of the time 30-45% of orexinergic cells were c-Fos+, a pattern normally seen only in wakefulness during dark phase or in stressful conditions. In all animals a dramatic overexpression of c-Fos was found in suprachiasmatic nucleus. Increased c-Fos-IR was seen in mediodorsal, supraoptic, paraventricular and arcuate hypothalamic nuclei, paraventricular and anterodoral thalamic nuclei and in many neocortical areas, including primary motor, anterior cingulate, retrosplenial, primary and supplemental somatosensory areas.
Conclusion: Changes in the activity of sleep- and wake-related neurons during SWDs show that in WAG/Rij rats absence-like seizures are associated with arousal. The study of sleep-related c-Fos-IR also revealed abnormalities in functioning of sleep and waking-promoting systems. We found elevated activation of orexinergic and histaminergic arousal systems, the absence of sleep-related changes in counts of c-Fos-IR cells in the VLPO and increases in sleep-related c-Fos-IR in the MnPN. We hypothesize that these abnormalities may produce imbalance in the ascending control of thalamocortical system leading to SWDs. In addition, dramatic changes in neuronal activation estimated by c-Fos-IR were found in nuclei involved in regulation of circadian rhythms and in neuroendocrine hypothalamic nuclei.

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The Sleep Promoting Effects of Gamma-Hydroxybutyrate (GHB) Are Partially Blocked by the GABAB Receptor Antagonist, CGP-35348

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Introduction: Administration of gamma-hydroxybutyrate (GHB) increases slow wave sleep and growth hormone release in both young and old humans. In rodents, we showed that GHB induces an initial period of EEG hypersynchrony in wake followed by an increase in NREM sleep time and slow wave activity. The specific GHB receptor antagonist, NCS-382, at a low dose (20-30 mg-kg) partially blocks the NREM promoting effect of GHB, however, GHB also interacts with gamma-aminobutyric acid (GABA) and dopaminergic systems. Here, we tested the hypothesis that sleep effects of GHB could be blocked by GABAB and GABAA receptor antagonists.
Methods: Pharmacological treatments were performed in adult (3-4 months) male Sprague-Dawley rats implanted with EEG/EMG electrodes for sleep/wake recording. First, i.p. injections of the GABAB receptor antagonist, CGP-35348 (15, 25, 50 and 100mg/kg) or the GABAA receptor antagonist, picrotoxin (.5, 1 and 1.5 mg/kg) were given to select the dose with minimal effects on sleep. Next, rats (N=5) underwent four injection conditions, (1) veh/GHB (200mg/kg) (2) veh/veh (3) CGP(15mg/kg)/veh and (4) CGP/GHB. For each trial, the first injection was given 30 minutes before lights out and the second at dark onset. This protocol was repeated in separate animals (N=4) using picrotoxin (.5 mg/kg). Hourly sleep-wake and EEG power spectra values between injection trials were compared using within-subjects ANOVA with follow-up post-hoc tests when indicated.
Results: GHB: In the first hour after veh/GHB injections, EEG activity in the delta frequency (0.5-5.0Hz) was increased during wakefulness (+ 238%, $p \leq .001$), compared to veh/veh. This phase was followed by a period of normal waking EEG patterns. In hour 2, NREM sleep time (+172%, $p \leq .02$) and NREM delta power (+134%, $p \leq .03$) were notably increased. NREM time was elevated in hour 3 (+197%. $p \leq .001$), whereas NREM delta power was non-significantly increased (+118%, $p \leq .10$). CGP-35348: Following the CGP/GHB combination, EEG hypersynchrony during wake was intermediate between veh/veh (+157% $p \leq .01$) and veh/GHB (65.7%, $p \leq .01$), indicating partial antagonism. Similarly, GHB-induced NREM sleep in hour 3 was partially blocked by CGP/GHB (+146% vs. veh/veh, $p \leq .01$ and 74% vs. veh/GHB $p \leq .001$). A trend occurred for CGP/GHB to reduce NREM delta power in hour 2 compared to veh/GHB injections (82%, $p \leq .10$), although this effect may require a larger sample to accurately interpret. Picrotoxin: None of the sleep effects of GHB were clearly blocked by picrotoxin (.5mg/kg).
Conclusion: We conclude that certain effects of GHB in rodents, such as waking EEG hypersynchrony, increased NREM sleep time and enhanced NREM delta power, may be mediated in part, through the GABAB receptor system. One possibility is that GHB directly interacts with the GABAB receptor, or that the endogenous conversion of GHB to GABA promotes the binding of GABA to its own receptors. We previously showed that GHB increases NREM sleep partially through interactions with specific GHB receptor sites. Low doses of CGP-35348 (15mg/kg), picrotoxin (.50mg/kg) and NCS-382 (20-30mg/kg) were used in these experiment and future studies will determine whether higher concentrations of the antagonists more completely block the sleep-inducing effects of GHB.

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Local Increase in Slow-Wave Activity after a Learning Task

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Introduction: In mammals, EEG slow-wave activity (SWA, 0.75-4.5 Hz) during non-rapid eye-movement (NREM) sleep is homeostatically regulated as a function of previous wakefulness. It has been suggested that SWA homeostasis may reflect synaptic changes underlying a cellular need for sleep (Krueger and Obαl, 1993; Tononi and Cirelli, 2003). If this were so, inducing local synaptic changes should induce local SWA changes, and these should benefit neural function. To find out, we used high-density EEG analysis to investigate local changes in SWA homeostasis after subjects performed a learning task.
Methods: Young male subjects (n=8) reached for visual targets using a handheld cursor while unconsciously adapting to systematic rotations imposed to the perceived cursor trajectory (rotation adaptation; Ghilardi et al., 2000) just before going to bed. At a week interval, they performed the same task without having to adapt to any imposed rotation (no-rotation). Sleep EEG was recorded during for 2-h using a Geodesics Sensor Net composed of 256 electrodes. The sleep EEG was staged, subjected to semi-automatic artefact removal and to power spectral analysis (4-s epochs, FFT routine, Hanning window). For anatomical localization, EEG electrodes were digitized and co-registered with each subject's magnetic resonance image.
Results: Sleep EEG power maps revealed a predominance of SWA over orbitofrontal and prefrontal cortex in both the rotation adaptation task and the no-rotation task. Contrasting the two tasks revealed increased SWA after rotation adaptation in a cluster of electrodes overlying right parietal cortex. MRI-aided localization of SWA increases highlighted Brodmann areas 40 and 7. The peak SWA increase, whose precise location varied slightly between subjects, amounted to 27.1±5.7% ($p<0.005$, paired t-test). The local increase in EEG power was most evident in the SWA frequency range and showed a decreasing trend within the first NREM sleep episode. Behavioral analysis showed that subjects training in the evening had improved task performance when retested after sleep, while subjects training in the morning did not improve when retested after 8 hours of wakefulness. Post-sleep performance improvement was strongly correlated with the local increase in SWA ($r=0.84$, $p<0.01$).
Conclusion: These results provide evidence that: i) SWA homeostasis can be induced on a local level. This finding is in line with earlier indications of use-dependent interhemispheric shifts in SWA power in humans and animals (Kattler et al., 1994; Vyazovskiy et al., 2000); ii) SWA homeostasis can be triggered by a learning task involving specific brain regions. The regions showing sleep SWA changes after rotation learning correspond precisely to those obtained in trained awake subjects using PET (Ghilardi et al., 2000) and are involved in visuo-motor transformations; iii) SWA homeostasis correlates strongly with post-sleep performance improvement. Thus, these findings add to the recent demonstration of a beneficial effect of sleep on task performance (Mednick et al., 2002; Walker et al., 2002; Fenn et al., 2003). Moreover, they suggest that the homeostatic regulation of sleep and the effects of sleep on plasticity may be closely linked.

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Role Of Leptin In Sleep Consolidation And Circadian Rhythmicity

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Introduction: Alterations in sleep architecture are associated with complications in cardiovascular, pulmonary, and metabolic systems. Clinical, epidemiological, and genetic studies have suggested interactions between pathways regulating sleep, endocrine physiology, and energy balance, but the molecular basis for these interactions is unclear. To test the hypothesis that metabolic regulatory pathways control sleep and circadian rhythms, we have examined the effect of leptin deficiency on sleep in the ob/ob mouse, a well-characterized rodent model of leptin-deficient obesity, hyperphagia, hyperglycemia, hyperinsulinemia, and insulin resistance. Our results demonstrate increased sleep fragmentation and decreased circadian rhythmicity in the ob/ob mouse compared to age matched wild type controls. These findings establish new evidence for interactions between networks controlling sleep and energy homeostasis.
Methods: For this study, twelve week old B6.V-Lepob (ob/ob) and wild-type control C57BL/6J (wt) male mice were placed on a 12L:12D cycle (lights on 6AM) and allowed food and water ad libitum. Animals were implanted with subcutaneous telemetry probes to measure body temperature and EEG/EMG electrodes for sleep/wake characterization. Polysomnographic recordings were continuously collected for forty eight hours. The second baseline day was visually scored in 10 second epochs as wake, NREM, or REM. Data are reported as mean ± sem, and statistical analysis was performed using a t-test to determine if differences between ob/ob and wt were significant ($p<0.05$).
Results: Over 24 hours, the percentage of total sleep time was significantly elevated in ob/ob mice when compared to wt (wt: 45.6±0.9% v. ob/ob: 49.1±0.5%, $p = 0.025$), due mainly to an increase in NREM sleep (wt: 40.7±1.1% v. ob/ob: 43.7±0.08%, $p=0.07$). Compared to wt controls, sleep in ob/ob mice decreased during the light phase (wt: 65.1±3.2% v. ob/ob: 60.1±1.8%, $p=0.06$), and increased during the dark phase (wt: 26.2±0.4% v. ob/ob: 38.2±3.2%, $p=0.003$) suggesting circadian disruption of the sleep/wake cycle. Similarly, dampened rhythms in body temperature were present in both light ($p=0.03$) and dark phases ($p=0.03$) in the ob/ob mouse. In addition to the changes in total sleep time in the ob/ob mice, there was an increase number of arousals (wt: 100.7±10.7 v. ob/ob: 161.3±4.8, $p = 0.005$) and stage shifts (wt: 590.7±42.3 v. ob/ob: 915.7±23.0, $p = 0.002$). Accordingly, the number of bouts were significantly increased for wake ($p=0.006$), NREM ($p=0.001$) and REM ($p=0.05$), and average bout duration was decreased for wake ($p=0.02$), NREM ($p=0.005$), and REM ($p=0.03$) in the ob/ob mouse.
Conclusion: We conclude that obesity and dysmetabolism in the ob/ob mouse is associated with increased sleep fragmentation and decreased rhythmicity of sleep/wake distribution and body temperature. These data provide new evidence for a link between sleep quality and the primary genetic pathways regulating mammalian energy balance.

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Fear Conditioning Increases NREM Sleep and NREM Delta Oscillations

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Introduction: To understand the role that sleep may play in memory storage, our work investigates how learning affects sleep. Our previous experiments have revealed that sleep deprivation selectively impairs contextual fear conditioning. Although many behavioral experiments demonstrate the necessity for sleep after learning, the molecular relationship between sleep and memory remains unexamined. To investigate the influence of sleep on memory, we have examined mice using fear conditioning—a task that is beginning to be understood in molecular terms.
Methods: Adult C57BL/6J mice (12-24 weeks of age) were implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes under isofluorane anesthesia. Mice were allowed two weeks recovery before recording. After allowing two weeks recovery from surgical implantation of EEG and EMG electrodes, mice were given 3 days to habituate to being handled for 5 minutes per day. On training day, mice either received context exposure for two minutes followed by a 30 second tone (sham group, n=15), context exposure followed by a 30 second tone and foot-shock at two and half minutes (fear conditioned group, n=16), or contextual exposure followed immediately by shock and tone (immediate shock group, n=12). 24 hours after training, mice were tested in the same context by evaluating the amount of freezing over a five minute period.
Results: Mice receiving fear conditioning froze 20 +/- 2 % during the five minute testing period, but mice receiving immediate shock treatment froze 4 +/- 3 % and mice receiving sham treatment froze 2 +/- 1 %. During the first 24 hours after training fear conditioned mice had 626 +/- 24 minutes of NREM sleep, immediate shock mice had 562 +/- 23 minutes, and sham treated mice had 546 +/- 22 minutes. In contrast, no differences were seen in REM sleep during the 24 hour period. Fear conditioned mice had 65 +/- 5 minutes of REM sleep, immediate shocked mice had 64 +/- 6 minutes, and sham treated mice had 62 +/- 5 minutes of REM sleep. Increased NREM sleep in fear conditioned mice was due to a decrease in wakefulness. Fear conditioned mice were awake 745 +/- 24 minutes, immediate shock mice were awake 811 +/- 21 minutes, and sham treated mice were awake 826 +/- 20 minutes. Because fear conditioned mice sleep longer than both sham treated mice and immediate shock mice ($p < 0.05$), our results suggest that the learning experience of fear conditioning, but not context exposure or shock experience alter sleep. Fear conditioned mice had more delta (1-4 Hz) after the training experience ($p < 0.01$), and increases in NREM sleep were correlated with increase in delta power ($p < 0.05$).
Conclusion: Single trial training for fear conditioning in C57BL/6J increases NREM sleep, but has no effect on REM sleep during the 24 hour period following training. Changes in delta power suggest that sleep homeostasis has been altered after the training experience.

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Penetration of Sensory Stimuli Across Sleep Spindles

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Introduction: The transition from wakefulness to slow-wave sleep (SWS) is associated with reorganization of the sensory input to the cortex. Despite the hypothetized interruption of sensory input at the thalamic level (Steriade M. and Timofeev I., 2003), there is evidence that it is preserved, although significantly modified (Velluti R. and Pedemonte M., 2002). Typical signs of brain electrical activity during SWS are sleep spindles, characterized by rhythmic periodic alternation of long lasting hyperpolarization with the rebound bursts of EPSP and periods of desynchronization between them. Such a cyclic/phasic organization of spindling lets us predict the possibility of sensory information penetration through the thalamus during SWS. To test this hypothesis we investigated the interaction between sensory input and spindling activity, using evoked responses (ERs) and high frequency oscillatory (HFO) responses 200-600 Hz across sleep spindles.
Methods: Two pairs of stainless steel screw electrodes were implanted on the rat sensory cortex. Random auditory clicks (1-2/sec) ERs were recorded continuously during 2-6 hours and analyzed post-hoc during 30 ms pre-stimulus and 250 ms post-stimulus epochs. Stimuli binned with the middle part of sleep spindles and inter-spindle intervals were analyzed. The amplitude of P1 peak from pre-stimulus baseline, inter-peak P1N1 amplitude, P1 and N1 peak latencies were then estimated. The amplitude of high frequency component was determined by FFT filtering ERs in 200-400 and 400-600 Hz bands.
Results: The average amplitudes of both P1 and P1N1 components of ERs showed a significant increase (55-63%, $p<0.05$) during spindles as compared with inter-spindle intervals. Separate analysis of rising and falling slopes of the spindle wave showed higher ER amplitudes (34-62%, $p<0.05$) on the rising slope as compared with the falling slope. Amplitude of ERs sharply increased on the trough of the spindle wave (P1 - up to 54.5%, $p<0.05$). Peak latency of P1 was shorter on the rising slope, than on the falling one (up to 27%). High frequency oscillations of both 200-400 and 400-600 Hz bands were larger (15 to 22%) during spindles compared with inter-spindle intervals.
Conclusion: Our results support the idea that sensory stimuli can penetrate to the cortical level during certain phases of sleep spindles. A sharp increase of ER amplitudes on the negative trough of the spindle wave may represent coincidence of the sensory stimulus with a period of rebound excitatory bursts in the thalamus, which occur at the beginning of cortical depth negative (i.e. surface positive) wave (Grenier F., Timofeev I., Steriade M., 1998). Higher values of ER amplitudes on the rising positive slope of spindle wave together with lower P1 latency may represent excitation of cortical elements, following the thalamic excitatory rebound burst (Grenier F., Timofeev I., Steriade M., 1998).

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Sleep Slow Oscillations as Traveling Waves: Origins and Pathways of Propagation in Humans

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Introduction: A slow (<1Hz) oscillation (SO) of the membrane potential of cortical neurons is the fundamental intracellular phenomenon underlying NREM sleep rhythms. In vivo and in vitro studies have thoroughly explored the cellular and network mechanisms underlying the SO. However, little is known about its large-scale, spatio-temporal dynamics. Specifically, no information is available about the synchrony, the diffusion and the modality of spread of the SO in the human brain.
Methods: We performed high-density (256 channels) EEG recordings (EGI, Oregon) in 6 subjects during the first sleep episode of two nights. All signals were digitized at 500 Hz, filtered (0.1-4Hz) and re-referenced to mathematically linked ears. A dedicated algorithm automatically detected the SO on the multi-channel signal. For each cycle of the SO, the time of occurrence of the negative peak was detected on all electrodes in order to calculate interpolated maps of latency. The electrode with the earliest relative latency was considered the origin. From the spatial distribution of the relative latencies measured at all channels we obtained the pathway of propagation for each cycle, which we characterized through streamlines.
Results: High-density recordings over large regions of the scalp showed that the SO is a traveling wave. The average time of propagation of the SO over the scalp was 115±9.9 milliseconds. Both the location of the origin and the direction of the propagation varied from cycle to cycle. Although virtually any electrode could be the origin of a cycle, a net preponderance of anterior origins was found: in all subjects, more than 50% (51.8±2.9) of the cycles originated from a region of the scalp anterior to electrodes F3 and F4. The digitalization and the co-registration of the electrodes with individual anatomical MRIs revealed a higher density of origins over the orbito-frontal cortex. The prevalent direction of propagation of SO waves was fronto-occipital. In each individual, both the location of the foci of high origin density and the prevalent direction of propagation were reproducible across nights.
Conclusion: The present findings indicate that single cycles of the sleep SO behave as traveling waves with identifiable origins and pathways of propagation. The individual distribution of the origins is reproducible and may reveal cortical foci of higher excitability or cortical pacemakers. The speed and path of propagation may reflect cortico-cortical connectivity. A systematic study of traveling waves during NREM sleep may provide useful information about the normal and diseased brain.

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Effects Of Neuropeptide S In The Regulation Of Sleep-Wake Cycle

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Introduction: Neuropeptide S (NPS) is a novel neuropeptide whose expression is restricted to a few hundred neurons in the locus coeruleus area. NPS shows no sequence homology to any known neuropeptide and it binds to its receptor with subnanomolar affinity. NPS receptor is widely expressed in the brain and its activation induces transient increases of intracellular Ca2 . Because NPS precursor is found mainly in brainstem nuclei and because this brain region plays an important role in the regulation of sleep, we determined the role of NPS on the sleep-wake cycle.
Methods: Eight male Sprague-Dawley rats were anesthetized with 2.5-3.0 % halothane and implanted for chronic sleep recordings as well as with a guide cannula in the lateral ventricle. One week after the surgery, rats were habituated to the recording conditions for at least 2 days. Rats implanted in the lateral ventricle were challenged with an icv microin-

jection of NPS peptide [0.1 and 1.0 nmol]. Polygraphic sleep recordings were analyzed for 6 hours following the injection. The SleepSign software (Kissei Comtec America, Irvine, CA) was used to score the EEG signal, and four stages were determined: wakefulness (W), slow-wave sleep 1 (SWS 1), slow-wave sleep 2 (SWS 2) and rapid eye movement (REM) sleep. Rats were housed individually with ad libitum access to food and water. The dark-light cycle was controlled (12:12). Statistical analysis of the data was carried out using an ANOVA and then a post-hoc Sheffe test. C-fos immunocytochemistry was conducted using a commercial antiserum (Oncogene Sciences 1:12,000) and visualized with DAB.

Results: A significant dose-dependent increase of W was observed one hour after treatment with NPS ($p < 0.01$), whereas the amounts of SWS1, SWS2 and REM sleep were decreased during the same period of time compared to their respective controls ($p < 0.01$). In contrast, two and four hours after NPS administration, the amount of SWS increased significantly ($p < 0.01$), compared to control animals, probably due to a rebound process. The increase in W was due to a significant increase in the number of episodes ($p < 0.01$, compared to their respective controls), whereas the increase in SWS was due to an increase in the duration of SWS episodes ($p < 0.05$). Injection of 1 nmol of NPS icv resulted in increased c-fos immunoreactivity in cortical and hypothalamic areas, consistent with the distribution of the NPS receptor.

Conclusion: Intracerebroventricular infusion of NPS causes a dramatic increase in wakefulness. c-fos immunoreactivity reveals that NPS activates several nuclei important in sleep/wake regulation. NPS defines a new cell group important in the regulation of the sleep-wake cycle.

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Microdialytic Perfusion Of Serotonin Into Perifornical-Lateral Hypothalamic Area Suppresses Wake-Associated C-Fos Protein Immunoreactivity In Hypocretin But Not In MCH Neurons

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Introduction: The neuropeptide hypocretin (HCRT)/orexin has been implicated in several physiological functions including sleep-wake regulation. In the brain, HCRT-containing neurons are localized within the PF-LHA among other neuronal types including melanin-concentrating hormone (MCH) containing neurons. HCRT and most other PF-LHA neurons are active during behavioral arousal and exhibit low activity during nonREM sleep. Evidence suggests that MCH neurons are active during REM sleep. Recent in vitro studies show that serotonin (5HT) may inhibit both hcrt and MCH neurons. In this study we examined the effects of microdialytic perfusion of 5HT into PF-LHA on the wake-associated c-fos protein immunoreactivity (Fos-IR) in hcrt , MCH , and other PF-LHA neurons.

Methods: Rats were implanted with EEG and EMG electrodes and a guide cannula for the implantation of microdialysis probe into the PF-LHA. The microdialysis probe was inserted at least 24 hrs before the recording session. The rats were kept awake while PF-LHA was perfused with either artificial cerebrospinal fluid (aCSF, n=4) or 5HT (n=4; 20mM) for 2 hrs during lights-off period and then sacrificed. The number of single Fos , HCRT , MCH , and double-labeled HCRT /Fos and MCH /Fos neurons were quantified on both ipsilateral and contralateral sides after aCSF and after 5HT treatments.

Results: Our preliminary data show that in response to 5HT perfusion during waking, the number of HCRT+/Fos+ neurons (mean±SEM) adjacent to the microdialysis probe decreased as compared to that observed after aCSF perfusion (% of HCRT+ neurons exhibiting Fos-IR, 10.6 ±4.53 vs. 52.36 ±4.96; p, <0.01). Compared to HCRT+ neurons, fewer MCH+ neurons exhibited wake-associated Fos-IR (2-3%) in response to aCSF perfusion. 5HT perfusion produced only marginal effects on Fos-IR in MCH neurons (% of MCH+ neurons exhibiting Fos-IR, 3.33 ± 0.91 vs. 1.71 ± 0.13). 5HT perfusion also increased the number of single Fos+ neurons (191 ± 38 vs. 152 ± 17).

Conclusion: Our preliminary data suggest that as assessed by wake-associated Fos-IR, 5HT inhibits HCRT neurons and excites a subset of non-HCRT neurons in PF-LHA. This is consistent with in vitro findings. The data further suggest that MCH neurons do not exhibit wake-associated Fos-IR and may not be responsive to 5HT during waking.

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Differential Effects Of Isoflurane And Halothane On Fast-Firing Midbrain Neurons

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Introduction: Previously, our laboratory has identified a population of midbrain neurons characterized both under halothane in the anesthetized animal and in the unanesthetized, freely-moving rat. These cells are remarkable in both preparations for their high discharge rates and short duration action potentials. This group of neurons has been linked to arousal mechanisms, and their properties in unanesthetized animals include a markedly state-dependent discharge profile, with higher discharge rates during periods of cortical arousal. Among the volatile anesthetics, isoflurane is now favored over halothane, primarily due to the greater hepatotoxicity of halothane. Previous comparisons between volatile anesthetics in various model systems have revealed effects on a number of electrophysiological parameters. In order to compare the effects of halothane and isoflurane on this population of cells we continuously recorded neuronal discharge rates in individual neurons in anesthetized animals while alternately delivering halothane or isoflurane.

Methods: Adult male Sprague-Dawley rats were initially anesthetized with halothane in an induction chamber, then tracheotomized and placed in a stereotaxic device. Core body temperature was maintained throughout the experiment at 37 degrees C. A skin incision was made and skull openings were made to permit access by glass micropipettes. Fast firing neurons in the red nucleus/VTA region of the midbrain exhibiting short duration waveforms were identified on-line, and firing rates derived from discrimination of individual action potentials were recorded on computer. A dual anesthetic vaporizer arrangement was used to cycle between halothane and isoflurane, delivering both agents in room air at a flow rate of 1L/min. Depth of anesthesia was assessed by pedal withdrawal response to pinch.

Results: Isoflurane concentrations required for adequate anesthesia were consistently lower than expected. Previous studies suggested higher minimal alveolar concentration (MAC) values for isoflurane than for halothane. In contrast, our data indicate that inspired levels of isoflurane required for a given level of anesthesia were consistently lower than those required with halothane. In addition, neuronal discharge activity under isoflurane was nearly 50% higher than at an equivalent anesthetic plane of halothane. Preliminary results also indicate that isoflurane may alter the firing patterns of midbrain neurons compared to halothane at equivalent depths of anesthesia. Isoflurane did not appear to affect action potential waveforms of the neurons studied.

Conclusion: The present results indicate that the discharge rate of arousal-related neurons in the midbrain differs markedly in the anesthetized animal, depending on the anesthetic agent employed. Specifically,

isoflurane, at equivalent depths of anesthesia, appears to depress neuronal discharge to a lesser extent than does halothane. These results are similar to those observed by others in cerebellar Purkinje cells recorded in vitro. The basis for the observed differences in effective anesthetic agent concentration remains to be identified.

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Facilitation Of Synaptic Responses In The Hippocampal CA3/CA1 Pathway During Carbachol-Induced Active Sleep In The Cat

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Introduction: During active (REM) sleep synaptic plasticity in the hippocampus increases compared to quiet (NREM) sleep (Bramham and Srebro, 1989). Based on these and related data, we were interested in determining if the hippocampal CA1 response to CA3 electrical stimulation, in conjunction with apnea, is altered during carbachol-induced active sleep (AS-carbachol) in the cat.
Methods: Experiments were performed on three adult cats. Surgical procedures to expose the dorsal hippocampus were carried out under isoflurane anesthesia. After the completion of all surgical procedures, the animals were anesthetized with α-chloralose (60 mg/kg, i.v.), or urethane (1.6 mg/kg, i.v.) and immobilized with flaxedil (1 mg/kg, i.v.). A recording microelectrode filled with 2M NaCl was placed into CA1 and a stimulating metal electrode was positioned into CA3. Episodes of ventilatory arrest (i.e., apnea; 1 to 1.5 minutes in duration) were conducted to produce a decrease in SpO2 similar to that which occurs in OSA patients (i.e., 50% SpO2). The synaptic efficacy of the CA3/CA1 pathway was examined prior to (control), during, and following apneic episodes using single-pulse, paired-pulse and tetanic stimulation. Thereafter, carbachol (0.25 μl, 4μg/μl) was injected into the nucleus pontis oralis (NPO) (P -3, L 1.5, H -4) to induce the state of AS-carbachol. During AS-carbachol, the experimental paradigms described above were repeated.
Results: Episodes of apnea that were conducted during control conditions (pre-carbachol) produced a 30-100% increase in the amplitude of the CA1 field potential response to CA3 stimulation; this increase lasted up to 10 minutes after the completion of the apnea episode. After the induction of AS-carbachol, in the absence of apnea, the baseline CA1 fEPSP induced by CA3 stimulation increased in amplitude by approximately 30%. During AS-carbachol in conjunction with apnea the amplitude of the CA1 response was 39-64% larger than the apnea-induced increase present during pre-carbachol condition.
Conclusion: These results indicate that the apnea-induced changes in synaptic plasticity in the CA3/CA1, i.e., potentiation of synaptic efficacy, is enhanced during AS-carbachol. Thus, we hypothesize that the excitotoxic mechanisms that are triggered in conjunction with obstructive sleep apnea are exacerbated during active (REM) sleep.

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Infusion of Brain Derived Neurotrophin Factor (BDNF) into Visual Cortex of Juvenile Rats Reverses the Effects of REM Sleep Deprivation (REMSD) on a Form of Developmentally Regulated Synaptic Plasticity

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Introduction: Previous work from this laboratory has demonstrated a role for REMS in developmental synaptic plasticity. BDNF is implicated in the neuroplasticity that is thought to underlie the critical period of development in the visual cortex. Inasmuch as BDNF expression in cortex is dependent upon neuronal activity and REM sleep (REMS) is characterized by high levels of brain activity, we propose that REMS may contribute to brain maturation through regulation of BDNF expression in visual cortex. We have recently observed an interim phase in rat brain development, starting after the usual end of the critical period and lasting until adulthood, when REMSD causes the resurgence of a developmentally regulated form of synaptic plasticity otherwise seen only in critical period animals. In these interim phase animals, theta burst stimulation (TBS) directed at the white matter (WM) produces long term potentiation (LTP) in layers II/III of the overlying visual cortex (referred to here as LTPWM-III). We hypothesized that exogenously applied BDNF would replace an essential neurochemical necessary for normal brain development, which is otherwise being blocked by ongoing REMSD. Accordingly, we infused BDNF into visual cortex of interim phase rats and tested whether BDNF would prevent the effects of REMSD on the ability of TBS directed at WM to induce LTPWM-III.
Methods: Five-week old rats were implanted with a cannula aimed at the binocular area of visual cortex on one side of brain. The cannula was connected, via a length of polyethelene tubing, to an osmotic minipump (Alzet, 0.5 L/hr) filled with BDNF (0.5 mg/ml, in PBS with 1% BSA). The tubing was pre-loaded with saline to prevent drug delivery during the postoperative recovery period and the two days of REMSD on multiple small pedestals over water. Accordingly, delivery of BDNF commences only at the start of the third and final day of pedestal REMSD. The opposite hemisphere was not implanted. At the end of the third day of REMSD (with BDNF infusion), each rat was sacrificed under gas anesthesia. The brain was rapidly retrieved and both treated and untreated hemispheres were cut in coronal sections (400 microns). Both hemispheres were prepared for in vitro synaptic plasticity studies and tested for LTPWM-III according to previously described methods. The stimulating and recording electrodes were positioned sufficiently far from the infusion site to avoid any injured tissue while being close enough to have been affected by the exogenous BDNF.
Results: LTPWM-III was reliably blocked in visual cortex on the side receiving BDNF infusions (8 of 8 attempts in 8 animals). In the opposite non-infused hemisphere, LTPWM-III was consistently obtained (6 out of 6 attempts), as would be expected after a period of REMSD in rats of this age. A control group of rats were infused with the saline vehicle solution (n = 5). We found that LTPWM-III could be obtained in either the saline- (5 of 5) or the non-infused visual cortex (3 of 3) in these animals.
Conclusion: Intracortical infusions of BDNF in REMS deprived, juvenile rats apparently restore the neurochemical processes that terminate the postnatal period for developmentally regulated forms of synaptic plasticity in visual cortex. Our results agree with previous reports that suggest a role for BNDF in ending the postnatal period for synaptic plasticity in the visual cortex. Furthermore, these results confirm our hypothesis that REMSD blocks BDNF expression in visual cortex of interim phase rats. The data also suggest that at some step in the neurochemical chain of events regulating developmental synaptic plasticity, REMS

facilitates BDNF expression in visual cortex and, in so doing, also contributes to the termination of the postnatal phase of developmental synaptic plasticity. These findings lends additional support for our proposal of a role for REMS in brain development.

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Effects of Drugs Affecting Blood Pressure and Heart Rate on The Release of Hypocretin in Normal Dogs

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Introduction: Deficiencies in the hypocretin/orexin (Hcrt) system are linked to narcolepsy. The normal function of Hcrt, however, is still unclear. The release of Hcrt-1 is closely linked to locomotor activity (Wu et al., Am J Physiol, 2002). The hypocretin system is also associated with autonomic functions. In this study we investigated the release of Hcrt-1 after the administration of drugs that affect heart rate and/or blood pressure in normal dogs while controlling locomotor activity.
Methods: Four normal Doberman pinschers were used in this study. They were first acclimated to a sling for 4 h each day for a week. The dog stood quietly in the sling, but could not locomote. On the day of experiment, the dog was put on the sling and blood pressure (BP) was measured every 2.5 min using an oscillometric non-invasive BP monitor with a cuff on the tail or the hindlimb. Heart rate (HR) was measured with 3 clip electrodes placed on the chest and limbs. Respiration was measured with a strain gauge placed around the chest. Measurements for the first 30 min were used as the baseline. Then, either atropine (45 μg/kg), methamphetamine (125 μg/kg), physostigmine (50 μg/kg), prazosin (40 mg/kg) or labetalol (0.25 mg/kg) was given i.v. A second dose was given 45 min thereafter except for prazosin whose effect persisted without supplementation. Resting in the sling for 2 h without drug treatment was used as the control. CSF (1.5 ml) was taken from the cisterna magna, 1.5 h after the initial dose, under thiopental anesthesia and assayed for Hcrt-1 as previously described (Wu et al., 2002).
Results: Methamphetamine, which enhances the release of dopamine and attenuates cataplexy in narcoleptic dogs, increased BP (10%) without significantly changing the HR, and produced a small increase in Hcrt-1 release (15%) in CSF as compared to the control condition. Atropine, a muscarinic antagonist that attenuates cataplexy, increased HR (44%) without changing BP, and had no effect on Hcrt-1 release. Prazosin, an α1 adrenergic antagonist that enhances cataplexy, produced a decrease in BP (9%) and an increase in HR (13%), and a moderate reduction in CSF Hcrt-1 (29%). On the other hand, labetalol, an α1 and β adrenergic blocker, which reduced BP (8%) and increased HR (9%), greatly increased the release of Hcrt-1 (42%). Physostigmine, a cholinesterase inhibitor that exacerbates cataplexy, reduced the release of Hcrt-1 (19%) and increased both BP (15%) and HR (14%).
Conclusion: The present study examined the relationship of autonomic functions and the release of Hcrt-1 in the CSF of normal dogs. The results suggest that there is no consistent relationship between changes in autonomic functions and changes in Hcrt-1 release. The increased release of Hcrt-1 after locomotor activity cannot be explained by changes in heart rate and blood pressure.

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Neurons of the Dorsomedial Pontine Tegmentum Make Synaptic Contacts with Caudal Pontomedullary Neurons Sending Ascending Projections to the Dorsomedial Pons

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Introduction: A discrete site has been identified in the dorsomedial pontine tegmentum from which REM sleep-like state can be effectively triggered by muscarinic cholinergic agonists and other drugs. However, studies also indicate that triggering of REM sleep from the dorsomedial pons requires intact connections between the pons and medulla. The goal of this study was to test whether neurons in the dorsal pontine REM sleep-triggering region have synaptic connections with medullary neurons whose ascending axons project to the dorsomedial pons.
Methods: In two rats, iontophoretic injections of the anterograde tracer, Phaseolus vulgaris leucoagglutinin (PHA-L) (35-42 μAmin) and pressure injections of the retrograde tracer, Fluoro Gold (FG) (25-40 nl), were made into overlapping sites centered within the dorsomedial pontine REM sleep-triggering region (AP -8.7 to -8.9 from bregma). After 12 days, rats were sacrificed and 25 μm coronal sections through the pons and medulla were immunohistochemically processed and then the tracers visualized using avidin-biotin-horseradish peroxidase histochemistry. Putative synaptic contacts between anterogradely labeled terminals (black) and retrogradely labeled cells (brown) were identified using a water immersion objective and counted in every eighth section caudal to the pontine injection sites.
Results: The estimated diameters of the effective uptake sites in the dorsomedial pons were 300-800 μm for PHA-L, and about 1200 μm for FG. The pontomedullary distribution of PHA-L-filled terminals was consistent with earlier similar studies. Most of the FG-labeled neurons with closely apposed PHA-L-labeled terminals (48 out of 67, or 72%) were located in the ipsi- and contralateral gigantocellular (23 cells) and ventral (10 cells) medullary regions, and in the caudal pontine reticular region (15 cells). This represented 3.2-5.4% of all FG-labeled cells in these three locations. Close appositions were present on both somata and proximal dendrites. Of the 48 FG-labeled neurons with close appositions, 63% had mean diameters less than 20 μm, 29% were of a medium size (20-30 μm), and the remaining 8% were larger than 30 μm.
Conclusion: These results reveal a simple reciprocal connection between neurons of the dorsomedial pontine REM sleep-triggering region and cells of the medial medullary and caudal pontine reticular formation. These connections may be mutually excitatory and play an important role in the triggering and/or maintenance of REM sleep. GABAergic cells with projections to the pontine REM sleep-triggering region were also observed in the same pontomedullary locations (Broissard et al., Eur. J. Neurosci., 18: 1627-1639, 2003), but it is not known whether they are innervated by fibers emanating from the dorsomedial pontine tegmentum.

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Regulation of Perifornical-Lateral Hypothalamic Area Neurons: Role of GABA and its Implication in Sleep-Wake Regulation

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Introduction: The perifornical-lateral hypothalamic area (PF-LHA) has been implicated in several physiological functions including sleep-wake regulation. PF-LHA contains a mixture of cell types including neurons containing the peptides, hypocretin (HCRT)/orexin and melanin-concentrating hormone (MCH). Most PF-LHA neurons are active during behavioral arousal and exhibit suppression during nonNREM sleep. The PF-LHA receives GABAergic inputs including those from putative sleep promoting GABAergic neurons in the preoptic area. GABA inhibits both HCRT and MCH neurons in vitro. The in vivo effects of GABA on HCRT and MCH neurons are not known. In this study we tested a hypothesis that increased GABA-mediated inhibition contributes to the suppression of PF-LHA neurons during nonREM sleep.

Methods: Rats were implanted with EEG and EMG electrodes and a with guide cannula for the implantation of microdialysis probe into the PF-LHA. Rats were maintained on 12h : 12h light dark cycle (lights on at 8.00 h). Experiments were conducted during lights-on period (12.00-15.00h), when rats spent significantly more time asleep. The microdialysis probe was inserted at least 24 hrs before the recording session. Different doses of a GABAA receptor antagonist, bicuculline (BIC; 10μM for 60 min, n=1; 20μM for 30 min, n=1; 20μM for 60 min, n=5) or aCSF (n=4) were microdialysed into the PF-LHA in undisturbed animals. The EEG and EMG activity were monitored for 2 hr from the arrival of aCSF or BIC into PF-LHA until the animals were sacrificed. The number of single Fos , HCRT , MCH , double-labeled HCRT /Fos and MCH /Fos neurons were quantified on both ipsilateral and contralateral sides to the probe after aCSF and after BIC treatments.

Results: In presence of BIC, the number of HCRT+ neurons (mean±SEM) exhibiting Fos-IR adjacent to the dialysis probe increased significantly and dose dependently as compared to that observed after aCSF perfusion (42.15±5.61% vs. 5.82±4.7%, $p<0.01$) or a comparable region on the contralateral side (42.15±5.61% vs. 5.74±2.37%, $p<0.01$) of the brain. BIC also increased Fos-IR in non-hcrt neurons (number of single Fos+ neurons, 216±36 vs. 51±29, $p<0.01$). BIC produced marginal increase in Fos-IR in MCH+ neurons around the probe (6.66±1.71% vs. 2.63±0.42%, p=0.08, n=4). The effect of BIC on Fos-IR was restricted to the ipsilateral side. Rats treated with BIC spent more time in active waking (43.89±2.97% vs. 17.71±7.23%; $p<0.01$), and less time in nonREM (25.58±6.7% vs. 52.05±3.93%, $p<0.05$), and REM sleep (2.07±0.71% vs. 6.94±2.12%, $p<0.05$).

Conclusion: The results suggest that microdialytic delivery of BIC into the PF-LHA increases Fos-IR in both HCRT and non-HCRT neurons and promotes arousal. The effect of BIC on Fos-IR was localized to the ipsilateral side and therefore is not an indirect effect of arousal. These results support the hypothesis that PF-LHA neurons are subject to increased endogenous GABAergic inhibition during nonREM sleep. However, as compared to other PF-LHA neurons, BIC induced minimal changes in Fos-IR in MCH neurons. This suggests that MCH neurons are not under strong GABAergic modulation during nonREM sleep.

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The Effects of Diethyl-Lactam on Rodent Sleep

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Introduction: Diethyl-lactam (3,3-diethyl-2-pyrrolidone), a gamma-butyrolactone derivative, has been shown to potentiate GABAA currents. Because of this action, diethyl-lactam has hypnotic and anticonvulsant properties. Unlike other gamma-butyrolactone derivatives, diethyl-lactam has a higher therapeutic index than ethosuximide, valproate, and Phenobarbital. In addition, diethyl-lactams sole anticonvulsant action has been shown to be the result of its GABAA receptor modulating properties. This differs from other gamma-butyrolactone derivatives in that other compounds in this class also inhibit Na currents, or reduce voltage dependent Ca2 and K currents. Data also suggests that diethyl-lactam has potent soporphoric (at low doses) and anesthetic properties (at higher doses) and shares properties of the drug gamma hydroxy butyrate (GHB). Little work has been done to investigate additional properties this drug may have. The purpose of this investigation was to document the effects of diethyl-lactam on rodent sleep architecture.

Methods: Four Sprague-Dawley rats weighing approximately 375 grams were given a 500mg/kg dose of diethyl-lactam dissolved in saline or a saline injection in a counterbalanced design. Electrodes for electrophysiological recording of sleep were implanted according to standard procedures. Sleep was analyzed for 24hours after exposure to diethyl-lactam or vehicle control. Sleep was scored manually for each animal. Since each animal served as its own control, the effects of the drug were compared to the data obtained during the vehicle injection for each animal.

Results: Diethyl-lactam significantly increased high voltage (HV) sleep for the first six hours compared to control recordings (mean epochs scored 109 ± 55 and 59 ± 17 $p<0.05$) respectively. HV replaced waking and paradoxical sleep (PS) was reduced during the first 5 hours. There was a slight rebound in PS six hours after the injection compared to controls. In addition, there were notable qualitative differences between HV in the treatment condition compared to the control condition. The amplitude of the HV waves were noticeably greater under diethyl-lactam treatment than the control condition. The presence of myoclonic jerks was noted as well under the treatment condition, which persisted into the fourth hour of recording in one of the animals.

Conclusion: Diethyl-lactam shares some properties with GHB and related gamma-butyrolactones. The most notable similarity is its ability to produce prolonged high-amplitude HV sleep. It differs from GHB in that PS is reduced dramatically under diethyl-lactam, while GHB has been shown to maintain a fairly normal PS architecture. This preliminary data suggests that diethyl-lactam may be a useful tool, not only as a sleep-inducing agent, but it may give more insight into the actions of GABA A and sleep.

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The Effects of Sleep Stages and Time-of-the-Night on Event Related Potentials During Sleep: Preliminary Results

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Introduction: Several event-related potentials (ERPs) have been identified during NREM sleep, including P220, N350, P450, N550, and P900. N350 and P900 were shown to be larger following target relative to non-target stimuli, suggesting the involvement of a discriminating process.

The amplitudes of these two components were also larger following sleep deprivation. It was hypothesized that they may reflect a sleep-related inhibition of incoming sensory information to facilitate initiation and maintenance of sleep. Most of the previous studies on N350 and P900 were conducted during daytime naps or around sleep onset. One recent study demonstrated that N350 was larger during light sleep relative to slow-wave-sleep. This study aims to further examine the effects of sleep stages and time-of-the-night on N350 and P900 throughout the night.
Methods: Five subjects (2 males, 3 females; mean age = 23.5) participated in the study. They slept in the sleep laboratory two nights. The first night served as a screening/adaptation night. Polysomnographic recording was conducted to rule out sleep disorders and to habituate the subjects to the laboratory environment. ERP recording was conducted throughout the second night. Brief 1000 Hz and 1500Hz tones (45ms, 60 dB), with a 1.5-s inter-stimulus interval were presented through a plug-type earphone. The probability of the target and non-target stimuli was 20/80. The subjects were instructed to count the number of target tones presented until they fell asleep. ERPs were recorded at Fz, Cz, and Pz.
Results: Three-way ANOVAs were conducted to compare N350 and P900 among different stages (stage1 vs. 2 vs. SWS), time of the night (first vs. second halves of the night), and type of stimulus (target vs. non-target). The results showed significant type and time-of-the-night main effects for both N350 and P900. Both components were larger following target stimuli and were larger during the first half than the second half of the night. There was also significant stage main effect and stage by type interaction for P900. Differences between target and non-target P900 were larger during SWS than stage 2 and stage 1 sleep.
Conclusion: The results showed a decrease of N350 and P900 over the night, indicating that the mechanisms of the two components may be related to the homeostatic regulation of sleep drive. However, P900 was further shown to be larger during SWS relative to light sleep, but N350 was not influenced by the depth of sleep. Although both components may reflect the sleep-related inhibition mechanism, N350 may be more an attention-prevention process that is sensitive to sensory input and P900 may be more a general inhibition process associated with the depth of sleep.

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Common Carotid Blood Flow Changes in Rem Sleep

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Introduction: According to previous studies, short-lasting bilateral common carotid artery occlusion exerts no significant influence on the spontaneous hypothalamic temperature increase characterizing REM sleep in cats and rabbits. This result suggests that brain cooling is depressed in this state of sleep as a result of a spontaneous decrease in the amount of common carotid artery blood flowing into the circle of Willis. The present study was aimed at obtaining direct evidence of the hemodynamic changes in the common carotid artery bed affecting cerebral circulation during REM sleep.
Methods: Adult rabbits (New Zealand) were used. Chronic implantation of i) extradural screw EEG and wire EMG electrodes and ii) a flowmeter, placed around a common carotid artery, was carried out under general (Clonazepam: 0.5 mg/kg i.m.; sodium pentobarbital: 40 mg/kg i.p.) anesthesia. Ear pinna temperature was also recorded by means of surface thermistors (Yellow Springs) since it indicates blood flow changes in the systemic heat exchangers of the head. The experimental sessions lasted 5-6 hours at 25±2°C in a sound-attenuated chamber. A Grass polygraph recorded the variables under study.
Results: During undisturbed NREM sleep, common carotid blood flow decreased slowly showing also small oscillations in amplitude. At REM sleep onset, common carotid blood flow either diminished further or remained unchanged with respect to NREM sleep. During the REM sleep episode abrupt and short-lasting surges of flow were also observed. A transient rebound in blood flow occurred on arousal from REM sleep.
Conclusion: These results reveal a conspicuous instability of blood flow in the common carotid artery bed during REM sleep and are consistent with a carotid blood "steal", at the expense of the circle of Willis, decreasing selective brain cooling during this state of sleep.

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Night Sleep In Native Brazilian Kaiowa-Guarani Adults

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Introduction: The subject of this research was to determine the night sleep pattern in Native Brazilian Kaiowa-Guarani adults. This is part of a broader research project that the authors are undertaken to determine sleep pattern and disorders in this ethnic group and other Native Brazilian population groups.
Methods: 120 subjects were analyzed (26 males; 94 females); 15-year-old ones and more; the mean age was 34.8 years old (sd=13.0); from a hamlet located in a Reservation in Dourados, in the south of the state of Mato Grosso do Sul, Brazil. A standardized sleep questionnaire was applied; with consent. The authors have no knowledge of previous literature on Kaiowa-Guarani sleep.
Results: The regular sleeping time at night was, on average at 8:48 pm (sd 2.88; variance 5:22). The usual wake up time in the morning was on average 5:36 am (sd 2:25; variance 5:53). On weekends, the sleeping time at night was on average 7:54 pm (sd 1:44; variance 6:53). The mean of waking up time in the morning in the weekends was 6:23 (sd 2:37; variance 6:51). Most of the population (N=76:120) woke up before 6:00 am. There was a trend to go to sleep earlier on weekends, and wake up later on weekends.
Conclusion: Night sleep pattern shown by this Kaiowa-Guarani population is similar to the pattern of rural population in other Native Brazilian groups like Terena and by Caucasian Brazilian rural population in Jaraguari, MS, both studied by the authors. On the other hand, the population here studied notably differs from urban night sleep pattern in middle and large cities in which sleeping time and waking up time are remarkably later due to socio-cultural factors and work time schedules. This research supports the relevance of epidemiological studies determining sleep patterns and disorders of Native Brazilian and the socio-cultural and ethnic influences.

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The Effects Of Natural Auditive Stimuli On Arousability During Sleep

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Introduction: Various studies using simple stimuli showed that the probability of the occurrence of arousal during sleep is related to sleep stages. This paper focuses on the study of arousability in various sleep stages by natural stimuli generated by passing vehicles.
Methods: Seven male subjects (20-30 yrs) slept in the laboratory for 2 nights a week during 9 weeks. The first week was a baseline week and in each week the first night was an adaptation night. Noise stimuli from airplanes, trains and trucks were recorded on tape and played back in the laboratory. During eight separate nights for each of the 3 noise sources 50 stimuli of 45 dB(A) or 15 stimuli of 65 dB(A) and in addition 15 train noise stimuli and 15 airplane noise stimuli of 75 dB(B) were presented randomly. EOG, EEG and EMG, ECG and sound level in dB were recorded. Sleep stages and EEG frequency bands were analyzed. An increase of post stimulus alpha and beta by a factor of 2 was defined as EEG arousal. The intensity of arousal was calculated as the logarithm of alpha plus beta amplitude. EEG arousals in pre and post stimulus periods, as well as in the quiet night were analyzed, using the method of pseudo stimuli. These pseudo or spontaneous arousal were tested against real arousals by logistic regression method.
Results: EEG arousals The distribution of EEG arousals over the various noise sources was different (Chi-square=46.8, p=0.000), whereas there was no difference in the intensity of the arousals. The probabilities of the occurrence of EEG arousals were higher for stimuli of 65 dB(A) than for stimuli of 45 dB(A). However 75 dB train stimuli did not show this effect. The mean intensity of EEG arousals was not different in the three conditions. Arousability A statistically significant pattern of decreased arousability was found for 45 dB(A) ($p<0.001$) and 65dB(A) ($p<0.05$) as the pre-stimulus sleep stage became deeper.
Conclusion: The probability of the occurrence of arousals with at lower stimulus intensity across sleep stages confirm earlier findings that stages 1 and 2 are lighter sleep than stages 3,4 and REM. At higher stimulus intensity, the arousal probability does not show equivocal effects, indicating that the interaction between arousability and awakening is complex. The intensity of arousal is not specific to sleep stages, irrespective of stimulus intensity or stimulus type. This is partially explained by the fact that arousals were quantified by alpha and beta frequencies only.

085

Scalp Topographic Mapping and Cortical Generators of the "Cyclic Alternating Pattern" (CAP)

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Introduction: The analysis of the so-called "Cyclic Alternating Pattern" (CAP) has been previously confined to its first-order time features. The significant technological advancements in computer of the last years allows now to record a large number of channels with a better representation of the EEG over the scalp, also during sleep.

Methods: We obtained all-night polysomnographic recordings including 19 EEG electrodes from 5 normal subjects who went to bed at their usual time and slept ad libitum.

Results: CAP has been characterized by 2 main frequency components: a slow component, which typically represents the A1 phase subtype of CAP and a fast component, typically detectable in the A3 phases of CAP. A2 phases, are characterized by a combination of these two components. The spectral analysis of these different A phase subtypes by means of the FFT supports the findings obtained by visual analysis and confirms their existence. For this reason, our following analyses have been focused on these two frequency components. The topography of the two bands has been studied by drawing colour maps of the scalp obtained by means of the so-called 4-nearest neighbours method. The low-frequency band (0.25-2.5 Hz) showed in all subjects included a clear prevalence over the anterior frontal regions, mostly over the midline and symmetrically spreading over the two hemispheres. On the contrary, the high-frequency band (7-15 Hz) involved mostly the parietal-occipital areas; also in this case, a symmetrical distribution was evident with the peak over the midline. In this band, a more variable distribution than that of the slow-frequency band was detectable in the different subjects. The analysis of the cortical generators of the two frequency bands of CAP was carried out by means of the "low resolution brain electromagnetic tomography" or LORETA in order to characterize better the structures responsible for the scalp electrical fields described above. With this approach, the generators of the low-frequency component of CAP seem to be localized mostly over the frontal midline cortex; on the contrary, those of the high-frequency band involve both midline and hemispheric areas within the parietal and occipital areas.

Conclusion: Synchronizing mechanisms during sleep are usually thought to be subserved by thalamocortical pathways and, as an example, there is experimental evidence that thalamocortical neurons may oscillate either in the delta or sigma frequency range depending on their membrane potential during nonREM sleep. We think that, based on our results, the CAP slow component is the cortical expression of this cortical-subcortical interaction. On the other hand, the high-frequency CAP component is the expression of the activity located at the level of the same structures thought to generate alpha waves during wakefulness within the cerebral cortex at the level of the pyramidal neurons in layers IV and V with a system of surface-parallel intracortical neurons involved in its spread. In conclusion, the results of these study and the data available on sleep neurophysiology seem to indicate that CAP is generated by the same intrinsic mechanisms of sleep and wakefulness which interact in a complex but highly integrated way.

086

Impaired REM Sleep By Alcohol Ingestion And Alcohol Sensitivity In Young Women

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Introduction: A large amount of alcohol taken before bedtime tends to shorten sleep latency, increase non-rapid eye movement (NREM) sleep and reduce rapid eye movement (REM) sleep in the first half of sleep. In contrast, the influence of a small amount of alcohol on sleep quality remains unclear. Electroencephalogram patterns induced by alcohol ingestion may be influenced by individual differences in alcohol metabolism. Accordingly, we investigated the effect of a small amount of alcohol on the sleep structures using polysomnogaraphy (PSG) with the sensitivity to alcohol using an alcohol patch test.

Methods: Thirteen healthy female students (age 21.1±0.7 years) were enrolled in this study. None of them had psychiatric, cardiovascular, metabolic, pulmonary or sleep disorders, history of drug and symptoms of excessive daytime sleepiness. Alcohol sensitivity was evaluated using ethanol patch test for all subjects. Absorbent cotton containing 100μl ethanol (40%) or the same volume of distilled water as a control was attached to the inner surface of upper arm for 7 minutes. The appearance of erythema 10-15 minutes after removal of the absorbent cottons was evaluated as "sensitive to alcohol" and the lack of erythema as "insensitive to alcohol". PSGs (ALICE 3; RESPIRONICS Inc, Pennsylvania, USA) were performed on three nights after one night for acclimation, and subjects consumed no alcohol (baseline night), 0.28 (alcohol night I) or 0.69 (alcohol night II) g ethanol/kg body weight, at 11 p.m. in approximately 30 minutes. The percentages of sleep time in each sleep stage of 1,2 3+4 and REM, REM latency, and REM cycle were calculated.

Results: In all subjects, there were no significant differences in all sleep parameters between baseline night and tow alcohol nights. Six of the 13 subjects were sensitive to alcohol, in whom, %stage REM was significantly decreased by alcohol consumption (baseline night: 18.3±6.2%, alcohol night I: 9.8±5.1% and alcohol night II: 11.0±2.8%), especially, %stage REM in the second half night was significantly decreased by alcohol consumption (baseline night: 28.5±9.4%, alcohol night I: 13.5±7.2%, alcohol night II: 16.2±3.3%), whereas there was no significant difference in the first half night. The REM latency was significantly prolonged (baseline night: 81.4±39.7min, alcohol night I: 162.8±37.9min, alcohol night II: 188.1±39.9min). The standard deviation of REM cycle was significantly greater on alcohol nights I and II than baseline night (52.1±25.5 and 68.5±21.1 vs. 26.7±11.9 min). There were no significant differences in other sleep parameters. In the other seven subjects who were insensitive to alcohol, none of the sleep parameters were significantly affected by alcohol consumption.

Conclusion: REM sleep was adversely affected by a small amount of alcohol in alcohol-sensitive healthy young women. Given REM deprivation leads to the impairment of concentration and memory, our findings suggest that a control of their drinking behaviors is important in order to have the good quality of sleep for alcohol-sensitive individuals. Alcohol sensitivity might play some important role in reduced REM sleep by an ingestion of a small amount of alcohol.

087

Effects of CNS Activation on Arousal and Autonomic Nervous System

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Introduction: EEG arousal involves cortical activation. Activation involves polysynaptic reflexes with incomplete responses, while arousal involves polysynaptic reflexes with complete responses and return to normalcy. Depending on CAP Stage, peripheral input results in varying responses in thalamic propagation, ascending gate, cortex, and sleep preservation. We evaluated the effects of CNS activation through auditory stimulation during sleep on arousal and autonomic nervous system responses.
Methods: Two groups (n =8, n = 6) of young, normal subjects were habituated to the sleep lab environment. Group 1 underwent incremental auditory stimulation starting at 60 dB to a maximum of 115 dB to induce a visual EEG arousal of 3 seconds. Group 2 underwent auditory stimulation set below threshold (65-75 dB [A]) for EEG arousals and Phases A2 and A3 of CAP. R-R interval and BP changes were measured. Mean sleep latency test (MSLT) and psychovigilance test (PVT) were performed the next day.
Results: In group 1, 343 ± 38 (mean ± SD) auditory stimulations were applied after stable Stage 2 NREM sleep, but only 198 ± 45 resulted in a visual EEG arousal. Stimulations that did not induce a visual EEG arousal resulted in K complexes (n =88) or no visible EEG changes (n = 55). The mean sound intensity was 91 dB. Auditory stimulation resulted in variable length of the mean RR interval, with the shortest interval associated with full awakenings. Heart rate increased by 10% compared to baseline without associated EEG arousal. Auditory stimulation associated with awakenings > 60 seconds in duration resulted in diastolic BP increase of 21.9 ± 9% and systolic BP increase of 28 ± 23%; stimulation associated with alpha EEG arousal resulted in diastolic BP increase of 19 ± 8% and systolic BP increase of 21 ± 14%; stimulation associated with K complex resulted in diastolic BP increase of 18 ± 8% and systolic BP increase of 13 ± 10%; and stimulation without accompanying visible EEG changes resulted in diastolic BP increase of 15 ± 8% and systolic BP increase of 12 ± 7%. The mean MSLT latency decreased from baseline of 15 ± 4 minutes to 8.8 ± 5 minutes post auditory stimulation night. In the 2nd group, a mean of 243 ± 11 stimulations resulted in mean EEG arousals of 13 ± 6; the mean number of times heart rate increased > 10% above baseline was 198 ± 19. The mean MSLT at baseline was 16 ± 1.8 minutes; post-auditory stimulation night mean MSLT latency was 16.4 ± 2 minutes. PVT did not show any significant change in the speed of response.
Conclusion: EEG arousal leads to autonomic nervous system changes — increase in BP and heart rate, with BP as a more sensitive parameter. Arousal resulted in sleepiness the next day. Auditory stimulation may induce activation of the brainstem without cortical arousal. There is dissociation between the EEG responses and the autonomic nervous system (ANS) responses. The role of the ANS responses is uncertain. Activation with subthreshold auditory stimulation did not result in either sleepiness or performance decrement.

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Sleep Related Slowing of LH Pulses in the Luteal Phase of the Menstrual Cycle

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Introduction: Pulsatile Luteinizing Hormone (LH) secretion is modulated very precisely across the menstrual cycle and slowing of LH pulses during sleep has been reported during the early follicular phase (Rossmanith JCEM 1987). LH pulse frequency decreases dramatically during the luteal phase, however, it is unclear whether sleep-related slowing of pulsatile LH also occurs in this phase of the cycle. As part of a study examining the effects of sleep disruption on menstrual cycle dynamics, pulsatile secretion of LH was studied during sleep and during wake in the luteal phase.
Methods: Four healthy young women (19-29 years) with regular menstrual cycles and on no medications affecting reproductive hormones or sleep were studied during a five-day inpatient stay during luteal phase (ovulation + 2 to 6 days). The first night (SP1) subjects slept for 8 hours at their habitual bedtimes. They were then awake for 24 hours. For the next three days, they slept for 8 hours beginning at their habitual wake-time and were awake for the remaining 16 hours. All sleep episodes were recorded polysomnographically and scored according to established criteria (Rechtschaffen and Kales, 1968). Blood was collected every 10 min through an indwelling catheter for two 16-hour episodes beginning at SP1 and again 48 hours later. Blood was assayed for LH using AxSym. Repeated measure statistics and paired t-tests were performed using SAS for Windows.
Results: Measures of sleep, including sleep latency and amounts of NREM sleep stages 1-4, REM sleep and Wake were not different between sleep at night and sleep during the day. The number of pulses was significantly different for the four different conditions (p=0.009): it was highest during wake-day (4.8 +/- 1.9 pulses /8 hours). Two subjects had no LH pulses during the sleep at night; one of these subjects also had no LH pulses during the sleep during the day. All subjects had at least one pulse during wake during the day or night. There were no significant differences between the three remaining conditions: sleep-night 1.8 +/- 1.2 pulses/8 hours; wake-night 2.3 +/- 1.3 pulses/8 hours and sleep-day 3.0 +/- 1.7 pulses/8 hours. There were significant differences in number of pulses between sleep-night and wake-day but not between wake-night and sleep-day collected 48 hours later. There were no significant differences in amplitude during the 4 conditions (p=0.82): amplitudes for sleep-night were 86.0 +/- 2.7 IU/L; for wake-day were 78.3 +/-27.2 IU/L; for wake-night were 105.6 +/- 19.6 IU/L; and for sleep-day were 87.0 +/-16.5 IU/L.
Conclusion: Night-time sleep-related slowing of pulsatile LH secretion occurred during the luteal phase. LH pulsatility was significantly faster during wake during the first 8 hours of the waking day than during sleep at night, sleep during the day or wake during the night. However, LH pulsatility slows across the luteal phase and therefore may contribute to the slower pulsatility observed during the wake-night condition. There were no changes in the average amplitude of individual LH pulses.

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Ventilation Response to an Arousal from Sleep is Independent of the Prevailing Level of CO2

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Introduction: Arousal from sleep is associated with transient respiratory activation. Historically this response has been understood to be a consequence of state dependent changes in respiratory control. The model predicts that the magnitude of the increase in ventilation at the point of arousal from sleep will be a positive function of the intensity of respiratory stimuli present at the time of the arousal. Further, it predicts that the level of ventilation achieved immediately after the arousal will be equivalent to the waking ventilation response to the prevailing stimuli. In order to test these predictions we assessed waking and stage 2 sleep PetCO2 ventilatory response curves, and the ventilation response to arousal from sleep, during various levels of PetCO2.
Methods: The subjects were five males between the ages of 18 and 22. Ventilatory response curves were determined by clamping PetCO2 at four levels during wakefulness and three levels during sleep (wake eucapnic, sleep eucapnic [low], and sleep eucapnic +3 [medium] & +6 [high] mmHg). A steady state was maintained for at least two minutes at each level before ventilation was assessed. Wakefulness values were assessed either in the afternoon, or on a separate night, while sleep values were collected over two experimental nights. The average number of measures for each subject at each level was 13 during wakefulness and 26 during sleep. In addition, the ventilation response to tone elicited arousal from stage 2 sleep was determined for each sleep level of PetCO2 (an average of 26 trials were conducted for each subject at each level). The magnitude of the response was defined as the difference between the last five breaths before the arousal and the largest value in the first three post arousal breaths. Arousals were required to meet the ASDA criteria and those that included body movements were discarded. Airflow was assessed via a nasal mask, pneumatotachograph and differential pressure transducer and converted to minute ventilation.
Results: The increment in ventilation at arousal from sleep did not significantly differ as a function of the level of PetCO2 present at the arousal ($p>.05$) and showed no consistent pattern over subjects. The average increments were 3.37 (1.63), 3.41 (1.79) and 3.6 (1.35) l/min for the low, medium and high levels respectively. Further, the magnitude of the ventilation response was substantially smaller than that that would have been predicted on the basis of the difference between the wake and sleep ventilation values for the respective PetCO2 values. These were 12.71 (15.53), 14.39 (16.47) and 16.89 (16.76) l/min for the low, medium and high PetCO2 levels respectively. Results were not affected by when the wakefulness values were collected.
Conclusion: The pattern of results was inconsistent with the view that the ventilation response at an arousal from due to a homeostatic response to prevailing respiratory stimuli, suggesting, by default, that it may be due to a reflex activation response.

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Does Frequent Arousal From Sleep Prevent the Sleep Related Fall in Blood Pressure in Young Healthy Individuals?

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Introduction: Sleep onset initiates large and abrupt falls in blood pressure (BP) and contributes to a fall in heart rate (HR). However, in severe hypertension and obstructive sleep apnea, the sleep related fall in BP is often absent (a non-dipping BP profile) and autonomic function is altered. In obstructive sleep apnea, this phenomenon is thought to be contributed to by repetitive arousals from sleep. The aim of this study was to determine whether frequent experimental arousal from sleep would retard the sleep related fall in BP and HR in young healthy individuals.
Methods: Ten young healthy males and females were maintained in a supine position and continuous BP, HR and pulse volume recordings were collected over two control nights and six experimental nights. On control nights, participants slept undisturbed for 90 mins, while on experimental nights they were administered repetitive tones during the first 90 mins of the sleep period following 2 min, 1 min and 30 sec of sleep. Two nights were administered in each of the three experimental conditions. Tone intensity was adjusted (70dB - 100dB) in order to produce arousals from sleep. The data were analysed as a function of five consecutive phases: 1) 30 min before lights out; 2) lights out to stage 1 sleep; 3) stage 1 to stage 2 sleep; 4) stage 2 sleep to the last micro-arousal before stable sleep for normal nights, (or the equivalent time for experimental nights); and 5) the first 20 min of undisturbed stable sleep for normal nights, (or the equivalent time for experimental nights). Data were analysed on a beat-by-beat basis and reported for 2 min periods in phases 1 and 5, and for 10% epochs in phases 2, 3 and 4 (as participants had variable time periods in these phases). Further, the cardiovascular response to arousal from sleep was analysed during phases 3 and 4 in the control condition (spontaneous arousals) and phases 3, 4 and 5 in the experimental conditions (tone induced arousals). Finally, the level during sleep prior to an arousal was analysed for each dependent variable.
Results: The total fall from pre-sleep wakefulness to the sleep phase was significant for BP and HR in all conditions (systolic BP: 9.9, 6.3, 8.1, 7.4 mmHg; diastolic BP: 6.8, 5.1, 4.6, 3.6 mmHg; HR: 9.0, 6.2, 7.8, 7.6 bpm, for the control, 2 min, 1 min and 30 sec conditions, respectively). Only systolic BP showed a significant interaction effect indicating a greater fall in the control condition, although differences between conditions were quite small. Analyses of the sleep periods prior to an arousal showed no significant differences between conditions in the magnitude of the fall in BP or HR across sleep onset.
Conclusion: Arousals from sleep had little effect on the underlying fall in BP and HR. Condition differences in systolic BP were a result of the direct transient arousal response being included in average values rather than in the underlying sleep related level of cardiovascular activity. Thus, in young healthy individuals, a simple auditory arousal stimulus did not impinge on the underlying sleep effect on BP and HR.

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A New Method of Analyzing Evoked Auditory System Activity During Sleep, Using Continuous Supra-fusion Stimulation

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Introduction: We present data utilizing a new method of studying auditory-system activity during sleep and wakefulness, which shows correlations with standard PSG staging, but also shows differences that may prove valuable. “Middle-latency” auditory evoked-responses averaged to brief repeated stimuli are usually elicited at stimulus rates below 10/sec because the responses can last up to 100 ms. Such rates are below

stimulus fusion (about 20/sec). A new stimulation and analysis method called QSD (q-Sequence Deconvolution) has been developed which permits recovery of the transient evoked-responses at rates as high as 100/sec despite response overlap. These responses are hypothesized to be a product of CNS processing of "background" sounds that are continuous, such as heating or cooling system noise. A series of 4-6 waves with periods in the gamma-frequency range are observed in the first 100 ms after tone-pip or chirp stimuli presented at 40/sec, which we call "G-waves". We have undertaken preliminary studies to determine whether these G-wave QSD-derived responses may have interest or utility to those interested in sleep research and/or clinical applications.

Methods: 20 adult subjects (ages 20-35, 40, 75) have been recorded over multiple nights. Standard polysomnograms were obtained, along with G-waves recorded from a different set of scalp electrodes (International 10-20 system). Both non-stimulation and stimulation nights were recorded in continuous overnight tracings in a sound-attenuating chamber. Stimuli were 30-50 dBSL tone-pips or chirps presented monaurally.

Results: G-waves were observed in all subjects. 1. G-wave changes between sleep stages: Grand mean waveforms for each sleep stage over an entire night, show a gradual reduction in G-wave amplitude but no consistent changes in latency. Individual subjects show reduced amplitude G-waves during sleep, compared with recordings before sleep. The deeper the SWS sleep, the lower the amplitude, but even in Stage 4 the waveforms were readily detected. 2. G-wave changes within sleep stages: There is some variation within stages. G-wave amplitude during REM was most variable sometimes approaching waking amplitude and at other times being as attentuated as in Stage 4. The variation within other stages was present but did not appear as great. 3. G-waves before and after sleep: Almost 3/4 of the subjects exhibited a reduction in G-wave amplitude between the control AWAKE recording prior to sleep, and the AWAKE recording taken in the morning immediately following arousal from sleep. 4. Because this is an exploratory study, in which correlations are sought between many variables, the Bonferroni correction for multiple comparisons makes it inappropriate to compute statistical probabilities.

Conclusion: The QSD methodology provides new information on the processing of auditory information during sleep. The G-wave amplitude decrement with depth of SWS suggests a number of hypotheses, one being that inhibitory processes in the auditory system may change as sleep deepens. The differences in G-waves in the pre- and post-sleep AWAKE recordings might indicate physiologic differences not detectable with standard PSG, and may have relevance for investigation of "sleep pressure" or the urge to sleep.

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Hypnotics Influence On Heart Rate Variability At High Altitude In Military Operational Conditions

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Introduction: In acute hypoxia exposure, resting heart rate (HR) and blood pressure (BP) have been shown to be elevated in non-acclimated subjects and the relationship between HR and exercise intensity to be shifted on the left. In addition, above altitude of 3000 meters, mountain climbers often complain of a poor sleep quality. Consequently, during climbing fatigue occurred faster than at sea level. To investigate changes in autonomic regulation of HR as a result of high altitude exposure, indexes of autonomic nervous system activity have been determined by spectrum analysis of HR variability (HRV) during postural changes. The sympathetic nervous system activity increases with tilt whereas the parasympathetic activity decreases. Moreover, sympathetic and parasympathetic modulation of resting HRV components has been described in overreached athletes. The aim of this study was to investigate in young healthy mountain climbers the efficacy of two hypnotics on sleep and their effect on resting HRV at high altitude in real operational conditions.

Methods: 12 young mountaineers spent 3 periods of 3 nights and following days at 3613 m of altitude (refuge of Cosmiques, France) with either 10-mg zolpidem (ZOL), 10-mg zaleplon (ZAL) or a placebo (PBO) given at 21:45 in random order according to a double-blind, 3-way crossover, controlled design. Periods were separated by at less 7 days of wash-out and the first period was preceded by a week at 800 m for control measures. Subjects waked up early in the morning and performed climbing all day long (about 7 hours exercise per day). At 05:00, resting HR and BP were measured, and saliva samples were collected in order to investigate cortisol, sDHEA and testosterone levels as indexes of fatigue. At 17:00, resting HRV was recorded during a stand-test (5 min supine, 5 min standing) with a Polar R-R recorder (Kimpele, Finland). Then, a hand-grip test was maintained during 1 min as endurance index. At night (21:30), resting HR and BP were measured.

Results: During the 3 periods at high altitude, cortisol level increased ($p<0.001$), indicating a high level of energetic expenditure while sDHEA and testosterone levels were not modified. There was no significant effect of treatment (ZOL or ZAL) vs PBO on biological samples excepted for cortisol that was higher under ZAL ($p<0.03$). Hand-grip force level increased as did the residual force of the endurance index ($p<0.05$). Hand-grip test was not affected by the treatment. Morning and evening resting HR and BP increased vs control ($p<0.01$). HRV analysis indicated in standing position an increase in low frequency (LF) component ($p<0.001$), and a decrease in high frequency (HF) component ($p<0.001$). LF/HF ratio reflected the increase of sympathetic modulation at altitude ($p<0.001$). There was no significant effect of treatment (ZOL or ZAL) vs PBO on HRV component.

Conclusion: In operational conditions, high altitude exercise was probably the major factor of HRV modulation. Hypnotic drugs do not show any deleterious effects on physical capacity, so that they could be safely used by climbers.

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Treatment Of Sleep Disturbances On Mountain At High Altitude: Zolpidem Versus Zaleplon Comparative Study

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Introduction: Above an altitude of 3,000 meters, mountain climbers often complain of a poor quality of sleep. Polysomnography shows an increase in stages 1 and 2 to the detriment of SWS. Sleep is also fragmented in combination with numerous apnea/hyperpnea episodes. As a result of sleep disturbances, daytime sleepiness and fatigue are often reported. Zolpidem and zaleplon have been shown to have positive effects on SWS without deleterious effects on ventilation during one night spent at a simulated (hypobaric chamber) altitude of 4,000 m. However, the efficacy of such hypnotics for mountaineers really exposed to high altitude is still unknown. The aim of the current study was to confirm the positive effects of zolpidem and zaleplon on sleep in mountain climbers at high altitude in real operational conditions.

Methods: 12 young healthy mountaineers spent one week at an altitude of 800 m (for familiarization with the methods then for control measures) followed by 3 periods of 3 treatment nights and following days at

3,613 m of altitude (refuge of Cosmiques above Chamonix, Alps, France) which were separated by at less 7 days of wash-out. The days following the nights were used for mountain activities. For each night, subjects were given either 10-mg zolpidem, 10-mg zaleplon or a placebo at 21:45 in random order according to a double-blind, 3-way crossover, controlled design. Lights were switched off at 22:00 for a 7-h period of sleep (22:00-07:00). Sleep and respiratory parameters were continuously recorded by respiratory polysomnography; arterial saturation in oxygen was continuously measured by infrared oxymetry. Sleep and altitude-related breathing events were analyzed according to standard criteria.

Results: To discard effects of daytime physical exercise on sleep, data obtained throughout the first night of each period are reported. Compared to control, stage 1+2 increased at altitude in placebo subjects (+16%, $p<0.01$) to the detriment of SWS (-32.3%, $p<0.001$), especially of stage 4 (-39.6%, $p<0.0001$) but not to the expense of REM sleep. Compared to the placebo group, zolpidem significantly increased SWS (+33.2%, $p = 0.004$), unlike zaleplon. Looking at sleep fragmentation, the number of arousals measured at altitude increased in the placebo group by 77% during stage 1+2 of sleep ($p<0.01$) and by 149% during REM sleep ($p<0.001$). Zolpidem and zaleplon reduced the effect of altitude on sleep fragmentation for REM sleep (+11% and +33% respectively, NS) but not for stage 1+2 (zolpidem: +84%, $p = 0.01$; zaleplon: +97%, $p = 0.04$). The expected effect of altitude on ventilation was confirmed with a significant increase in the apnea/hypopnea index in the placebo group ($p = 0.04$). This increase was not observed under zaleplon ($p = 0.10$, NS) and zolpidem ($p = 0.07$, NS) so that neither zolpidem nor zaleplon affected the control of breathing.

Conclusion: Both zolpidem and zaleplon have positive effects on altitude-related sleep and respiratory disturbances, with a more pronounced effect on SWS for zolpidem. Moreover, both hypnotic drugs do not show any deleterious effects on ventilation, so that they could be prescribed to climbers with safety.

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Effects Of Music On The Sleep State-Dependent P50 Potential And Frontal Lobe Blood Flow

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Introduction: The "Mozart Effect" is used to describe 1) that listening to music composed by Mozart heightens performance on certain spatial tasks, or 2) the intellectual advantage conferred by musical training, with the greatest effect seen in those whose training is initiated at an early age. It was postulated that the first, more transient, "Mozart Effect" could be due to raising the state of arousal. The P50 potential is generated, at least in part, by elements of the reticular activating system (RAS). P50 potential amplitude can be used as a measure of level of arousal, while the ratio of the second P50 potential to the first, in a paired stimulus paradigm, can be used as a measure of habituation. We also recorded relative frontal lobe blood flow using Near Infrared Spectroscopy (NIRS).

Methods: Subjects (18-68 yo) with no musical training (NoTr, n=10) or with musical training beginning before the age of 7 (Tr, n=15) underwent Control recordings followed by recordings during either 10 min of Mozart piano concertos (M) or of silence (S), in random order. The P50 potential was recorded and analyzed as previously described, while NIRS levels were recorded continuously.

Results: There was no difference in age between groups. The amplitude of the P50 potential for both NoTr and Tr groups together (n=25) was similar in Control 1.8+/-0.4; M 1.4+/-0.5; and S 1.5+/-0.5 (mean+/-SE in uV); while habituation also was similar in Control 15+/-8; M 24+/-9; and S 22+/-8 (mean+/-SE in %). The Tr group showed that P50 potential amplitude (Control 1.4+/-0.3; M 1.4+/-0.4; and S 1.3+/-0.5) and habituation (Control 19+/-8; M 29+/-9; and S 17+/-9) were similar to the NoTr group P50 potential amplitude (Control 2.0+/-0.3; M 1.4+/-0.5; and S 1.3+/-0.5) and habituation (Control 19+/-11; M 26+/-18; and S 30+/-19). NIRS levels for all subjects were Control 72+/-3; M 70+/-2**; and S 70+/-3*, with both decreases being statistically lower (*$p<0.05$; **$p<0.01$). NIRS levels for Tr subjects were also lower during M and S (Control 74+/-4, M 71+/-4* and S 72+/-4*), while NoTr subjects were lower during M (Control 70+/-3, M 68+/-3*, and S 68+/-3).

Conclusion: Our results show that exposure to music (Mozart piano concertos) 1) does not increase arousal, and may decrease it marginally, 2) has little effect on habituation to repetitive stimuli, and may decrease it marginally, and 3) leads to a relative decrease in frontal lobe blood flow. These effects were similar in untrained and musically trained subjects, indicating that, if there is a "Mozart Effect", it is unrelated to arousal level or pre-attentional function. However, the induced decrease in frontal lobe blood flow helps explain the "emotional" response to music, i.e. hypofrontality, although the mechanism behind this effect remains to be determined.

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Tonic Excitatory Drive to Central Respiratory Neurons in REM Sleep in Cat

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Introduction: Breathing in REM sleep is rapid, irregular and intermittently unresponsive to regulatory stimuli. An internal drive may be responsible for this. In cats, rhythmic or tonic diaphragmatic activity appears in REM sleep during ventilator-induced apnea. This activity appears several seconds to a minute after the onset of REM sleep, and it is episodic. Here we report the results of studies of respiratory neurons during REM sleep under conditions of ventilator-induced apnea. We hypothesized that an internal drive excited respiratory neurons of all types in REM sleep and that this drive was intense and nonreciprocal and therefore could disorganize breathing and lead to hypoventilation.

Methods: Adult cats underwent the following procedures: Implantation of electrodes for recording sleep-wakefulness and diaphragmatic activity; creation of a tracheal fistula; attachment to the skull of a headcap that contained standoffs for atraumatic head-restraint and a connector for electrodes; and an occipital craniotomy. After recovery from surgery and adaptation to the laboratory (a period of weeks), subjects were swaddled in a veterinary bag; their heads were atraumatically restrained; and the trachea was intubated through the fistula. A microelectrode was lowered through the craniotomy into the ventral respiratory group of the medulla. Extracellular recordings of the action potentials of single respiratory neurons were obtained 1) during spontaneous breathing in REM sleep and 2) during ventilator-induced apnea in REM sleep. The ventilator gave 50 ml tidal volumes at a rate of 50 per minute. End-tidal CO2 was maintained constant at 85% of the threshold for breathing by a computer controlled CO2 injector. Median discharge rates were determined during eupnea in NREM and REM sleep and during apnea in NREM and REM sleep.

Results: A total of 68 respiratory neurons from 3 cats was recorded in relaxed wakefulness, NREM and REM sleep. Inspiratory neurons (n=48) of all types (preinspiratory, decrementing, constant-throughout, and augmenting) were more active in REM sleep during both sponta-

neous breathing and ventilator-induced apnea than in NREM sleep ($p<0.05$, Student's t-test). Expiratory neurons (n=20) of all types (inspiratory-expiratory, augmenting and decrementing) tended to be more active in REM sleep during spontaneous breathing and ventilator-induced apnea, but the only statistically significant increase was for the population of inspiratory-expiratory neurons during spontaneous breathing. REM-specific excitation of individual neurons and of the diaphragm during ventilator-induced apnea were at times independent, and elements that discharged during different phases during eupnea were activated at times simultaneously. Activity in REM sleep across all cell types, inspiratory and expiratory, was 152% (63, sd) of the NREM rate during spontaneous breathing and 336% (710, sd) of the NREM rate during ventilator-induced apnea. Median discharge rates in REM sleep during ventilator-induced apnea were equal to or greater than discharge rates during spontaneous breathing in NREM sleep.
Conclusion: Internal tonic excitatory drive affects all respiratory cell types in REM sleep. The drive is intense and episodically nonreciprocal. Therefore, this drive, although excitatory, could disorganize breathing and account in part for the oxygen desaturation that occurs during REM sleep in patients with lung disease.

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Skin Sympathetic Activity during Human Sleep: a Laser Doppler Flowmetry (LDF) Study

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Introduction: It is commonly accepted that during NREM sleep the sympathetic outflow gradually decreases reaching the lowest level in slow waves sleep (SWS), whereas during REM sleep it changes phasically. However the sympathetic activity may vary depending on the specific function considered. While the muscle sympathetic nerve activity during sleep has been extensively studied, the skin sympathetic nerve activity (SSNA) SSNA, which includes the sudomotor and the vasoconstriction activities, has not been carefully assessed. The sympathetic regulation of cutaneous blood flow (CBF) during wakefulness differs from cranial to limb districts. The aim of the present study was to assess the following parameters in both cranial and segmental districts during sleep: mean CBF, spontaneous phasic sudomotor and skin vasoconstriction activities, as well as vasodilatatory response to local termic stimulation. Furthermore, we sought to evaluate the regional differences in the aforementioned parameters.
Methods: Fifteen healthy subjects, aged 20-35 years, have been studied in the sleep laboratory after one adaptation night. The study has been conducted in a sound-proof room kept at constant temperature (25 °C). The following parameters has been recorded during a eight-hour nocturnal polysomnograpy: EEG, EOG, submental EMG, oronasal flow and thoracic-abdominal efforts, forehead and fingertip CBF (using Laser Doppler Flowmetry or LDF), forehead and hand sudomotor galvanic response (using surface electrodes), EKG, skin temperature and continuous digital blood pressure (Portapress). During each sleep stages the vasodilatatory response to thermal stimulus was assessed by LDF.
Results: After sleep onset, phasic spontaneous vasoconstriction and sweating events occurred. The frequency of the sudomotor events increased gradually from the stage 1 to the stage 4 of NREM sleep, while during REM sleep no phasic sweating was observed. This pattern of sweating was similar in both limb and cranial districts. An opposite pattern was found for the skin vasoconstriction events: their frequency was very low during the slow waves sleep, increased during S1-S2 NREM and was highest during REM sleep. The majority of fingertip vasoconstriction events were temporally related to forehead vasodilatation. No significant differences were found in the mean CBF across the sleep stages. The limb response to the local thermal stimulus was preserved during all the sleep stages. During S2 NREM sleep a significant correlation between the phasic vasoconstrictions and the number of K complex was found.
Conclusion: this study showed that the sympathetic activity during sleep is heterogeneous, and that the sudomotor regulation is markedly different from the vasomotor one. During sleep, as well as during wakefulness, the limbs vasomotor regulation is different from the cranial one. The peripheral response to thermal stimuli is not influenced by the sleep-induced central autonomic modulation. The increased sweating, associated to vasodilatation during the SWS, may reflect the physiological thermodiffusion process typical of sleep. Conversely, the thermal diffusion is almost abolished during REM sleep. The differences between sudomotor and vasomotor activity could be not detected by the conventional microneurography that evaluates the global sympathetic skin activity. The LDF the technique allows a precise, continuous and not invasive monitoring of the CBF during sleep.

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Comparison Of Eye Movement In Stage REM To Eye Movement At Sleep Onset

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Introduction: The trajectories of slow eye movement (SEM) at sleep onset approximate not only continuous sinusoid waveforms ($y = \sin x$), but also more complex operations on a prototype function $y = f(x)$. It has been shown, for example, that local trajectories of hypnagogic SEM may approximate: (1) reflection around the y axis: $y = f(-x)$ (2) reflection around the x axis: $y = -f(x)$ (3) vertical translation: $y = f(x) \pm c$; $c>0$ (4) horizontal translation: $y = f(x - c)$; $c>0$; (5) stretching: $y = cf(x)$ or $y = f(x/c)$; $c>1$; It has been shown, in addition, that SEM waveform transformations (a) operate singly, serially, or by superposition; (b) may be static, with the y axis fixed, or dynamic, with a rightward-shifting axis of reflectional symmetry; and (c) are locally optimal and globally most dynamic in Stage 5/6 of sleep onset. Best fits to the mathematical transformations occur where SEM is optimally formed: inchoately saccade-like, with high values (as r2) of the amplitude × velocity main sequence. The present study provides preliminary evidence that eye movement in Stage REM displays similar structural characteristics.
Methods: Using BIOPAC TM hardware and software, DC electrooculography (EOG) was completed in five young adult subjects during nighttime sleep after adaptation to the laboratory. Using established measurement criteria for the EOG and the EEG, SEMs were counted at opposed, inversely matched deflections of the right and left EOG tracings during successive periods of Stage REM (REMPs). The vertical EOG was recorded for comparison. To remove EEG artifact the raw EOG was FIR low-pass filtered locally at frequencies commensurate with eye velocity. EOG waveforms were then displayed as eye position; as eye velocity (the derivative of eye position); and as the integrand of curve length, assigning positive values to velocity in either direction of eye movement. To assess the structure of REM, each tracing was then segmented according to successive segments' goodness of fit to any of the mathematical transformations listed above. DC baseline drift was subtracted from each REMP.
Results: Preliminary analysis suggests that: (1) Adjusting for higher eye velocities, REM trajectories operate on structural "templates" similar to those evident in hypnagogic Stage 5/6, and may conform to any of the mathematical descriptions that characterize SEMs. (2) REM bursts, like SEM sequences in hypnagogic Stage 5/6, are not homogeneous. Within

each REMP, REMs wax and wane in amplitude, velocity and structural complexity. (3) The longer the REMP, the finer the local articulation of both eye displacement and eye fixation. (4) Long REMPs display not only DC voltage drift but also intrinsic displacements of baseline eye position. (5) Both independent vertical eye movement and nystagmoid eye movement are more prominent in Stage REM than in hypnagogic Stage 5/6.
Conclusion: Eye movement at sleep onset and in Stage REM displays similar "template" morphologies. Higher eye velocites, nystagmoid REMs, and independent vertical REMs reflect greater excitation—and lower levels of inhibitory neuromodulation—in oculomotor neural networks in Stage REM than in hypnagogic Stage 5/6

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Autonomic and other Physiologic Changes at Wake Sleep Transition
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Introduction: The central regulation of autonomic function changes dramatically between wakefulness, REM and NREM sleep. These changes can be evaluated by means of time dependent analysis of instantaneous heart rate (HR) in the frequency domain. The aim of this study was to characterize and quantify the autonomic changes involved in the process of SO along with additional well defined physiological changes occurring around SO: electrical activity of the brain, respiration, skeletal muscle activity.
Methods: The study included 3 groups of subjects: normal (12), OSAS patients (11) and patients with Various Sleep Disorders VSD (11). All underwent standard whole night PSG. Time frequency decomposition of HR, respiratory frequency, surface EMG (mean rectified EMG reflecting the amplitude of the signal) and EEG activity (power in the frequency range of alpha and delta) were calculated along a time period starting 10 minutes before and ending ten minutes after the initiation of unequivocal stable sleep. The time frequency spectral analysis of HR supplied three parameters as follows: Very Low Frequency (VLF) and Low Frequency (LF) reflecting both sympathetic and parasympathetic activity and a High Frequency (HF) component that reflects mainly parasympathetic activity. The autonomic balance was supplied by the LF/HF ratio. Statistical analysis was performed by means of one-way ANOVA.
Results: SO as defined by standard criteria best coincided with a decrease of alpha power below 28% of total brain activity power. This was used as a reference time point for inter-subject comparisons. A parallel increase in delta EEG power was detected. Muscle activity expressed by mean rectified EMG displayed an unequivocal steep decrease at SO ($p<0.001$, $p<0.05$, $p<0.0001$, for normal subjects, OSAS, and VSD respectively). A decrease in the variance of respiratory frequency occurred around SO ($p<0.005$, $p<0.01$, $p<0.0001$ respectively). The autonomic parameter VLF displayed a consistent decrease with SO in all groups ($p<0.0001$, $p<0.05$, $p<0.0001$, respectively). LF power did not change significantly in OSAS patients, but displayed significant or near significant decrease in the other 2 groups. HF power did not change significantly in any of the groups.
Conclusion: The use of modern digital polygraphs allow to acquire high quality physiologic signals and their mathematical analysis reveals important previously neglected information on the physiology of SO. Thus we found a consistent decrease in respiratory frequency. A significant change in the amplitude of muscular activity was also found. Autonomic activity at the wake sleep transition is affected by the same underlying mechanisms that govern the process of SO. It fluctuates towards the period of SO and reaches a minimal value during that period. Differences between groups can be explained by higher sympathetic activity within the OSAS group. Changes in respiratory frequency and minute ventilation can account for the surprising lack of change in HF power, although parasympathetic activity is known to increase during NREM sleep. Monitoring autonomic activity can provide an additional indicator of the transition from wakefulness to sleep.

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Thermal Biofeedback And Sleep: Limited Effects And Methodological Challenges
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Introduction: Recent interest in peripheral temperature and sleep onset latency (SOL) has encouraged us to pursue our attempts to use thermal biofeedback to manipulate both core and peripheral temperature and explore its effects on SOL and sleep architecture. We summarize here the main results we obtain thus far.
Methods: First, 11 subjects were trained to use a biofeedback technique to increase and decrease their hands temperature (HT). Additionally, three subjects were trained to self-regulate their oral temperature (OT). Subjects from the OT condition and three subjects from the HT condition were successful enough in their training to be asked to apply the technique before sleep initiation, and their sleep was recorded over several nights (1 adaptation, 1 baseline (BSL), and 2 experimental nights (EXP) for each attempt to increase and decrease temperature). Rectal temperature (RT) was recorded during nocturnal sleep as well as in most of the training sessions.
Results: HT manipulation at bedtime: Eight subjects were not able to alter significantly their HT following at least four training sessions. Only one participant (previously reported) was successful in increasing his HT by a substantial amount (14°F to 18°F) at bedtime. This was accompanied by a 0.5°F to 0.7°F decrease in RT, and a decrease in SOL (BSL = 19.5 min., EXP = 11.5, and 5 min.). In addition, an increase in SWS% was noted (BSL = 11%, mean EXP = 13.75%), which was compensated by a decrease in % of stage 2 sleep (BSL = 58%, mean EXP = 51.5%). The other two participants were not successful in manipulating their HT at bedtime (mean$\uparrow$= 5.30°F, mean$\downarrow$ =3.70°F), and there was no effect on SOL. However, the relatively small HT decrease they achieved was followed by an increase in SWS% (BSL = 15.1%, EXP = 19.5%) in the first third of the night. No change in SWS% was found following their increase in HT. OT manipulation at bedtime: All three participants had difficulty self-regulating their OT at bedtime. Instances when they slightly increased or decreased their OT (mean$\uparrow$ = 0.08°F, mean$\downarrow$ = 0.27°F) were accompanied by a slight decrease in RT (mean$\downarrow$ = 0.19°F), but no systematic change in SOL or sleep architecture was noted.
Conclusion: The efficiency and potential of thermal biofeedback are more complex than previously thought. First, self-regulating OT seem to be more difficult than self-regulating HT, which is also not mastered easily (eight trained subjects and four participants were unsuccessful). In both cases, self-regulation seem more difficult to achieve at bedtime than during the afternoon or early evening. Furthermore, except for the one subject who significantly changed HT, RT was not affected significantly (even in training sessions). These results suggest that presleep HT and OT biofeedback has little effect on SOL and/or subsequent sleep architecture. Larger changes in HT or OT may be required to cause a sustained effect on RT and sleep. Finally, external manipulations (warm bath, thermal suit, etc.) may be more effective than internal (self-regulating) manipulations.

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Serotonergic Antidepressants Are Associated With REM Sleep Without Atonia

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Introduction: REM sleep behavior disorder (RBD) is generally observed in older men and in individuals with specific neurologic diseases. There are case reports of RBD in individuals taking serotonergic antidepressants. Our objective was to assess EMG activity during REM sleep in individuals taking serotonergic antidepressants and in a matched control group not on such medication.
Methods: Fifteen subjects referred to assess sleep-disordered breathing taking a serotonergic antidepressant and 15 age-matched individuals not on such medication were retrospectively identified. Subjects with an apnea+Hypopnea Index (AHI) >15 per hour (or REM-related AHI > 10), history of abnormal behavior during sleep or abnormal behavior on polysomnogram, active neurological disease, or taking benzodiazepines, antipsychotics or anticonvulsants were excluded. Primary outcome variables were submental and anterior tibialis tonic and phasic EMG activity during REM sleep as previously described by Lapierre and Montplaisir. REM latency and REM time, apnea-hypopnea index, periodic leg movements of sleep index, sleep architecture measures were identified as related variables.
Results: Tonic submental EMG activity during REM sleep was significantly more common in the antidepressant treated group than the control group ($p<0.02$). Tonic REM submental EMG activity correlated with REM latency ($r=.42$, $p=0.02$) and inversely with REM time ($r=-.36$, $p=0.05$). Subject age correlated with tonic REM submental EMG activity ($r=.58$, $p=0.02$) in the antidepressant group. There was no correlation between REM submental EMG tone and antidepressant dose. There were also trends for more phasic activity in the anterior tibialis ($p=0.09$) and submental ($p=0.07$) EMG in REM sleep in the antidepressant group than in the control group. There was a negative correlation between such phasic activity in the anterior tibialis and REM time ($r=-0.42$, $p=0.02$).
Conclusion: Our results demonstrate that serotonergic antidepressants are associated with a statistically significant reduction in REM sleep atonia, even in individuals without overt clinical features of REM Behavior Disorder. Although the clinical significance of REM sleep without atonia has not been established, there are substantial potential public health implications of REM sleep abnormalities in individuals taking serotonergic antidepressants.

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Heart Rate and QT interval Variability During Placebo and Caffeine Sessions: Increased Sympathetic Activity during REM after Caffeine

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Introduction: A number of studies have shown that administration of caffeine in the evening produces poor sleep. Other studies have actually used caffeine to successfully model psychophysiological insomnia. Further, it is known that patients with insomnia have characteristic EKG changes, including increased heart rate, increased sympathetic activity, and decreased parasympathetic activity. It was hypothesized that similar changes in cardiac activity would occur after administration of caffeine to young adult normal sleepers.
Methods: Fifteen young adult normal Ss slept in the laboratory for several nights prior randomization into a caffeine protocol where Ss received caffeine 400 mg 30 min prior to one night of sleep and placebo randomly prior to another night. Standard EEG and EKG leads were recorded on all nights on paper and into a Grass Braintree digital recording system using Grass Gamma Software (version 2). The data were sampled at a rate of 500 Hz. Data samples of 256 second periods of the EKG trace were taken from wake (before sleep), stage II and REM for placebo and caffeine conditions. A peak detection algorithm was used to identify the R-R intervals (in milliseconds) from the EKG. A common QT variability algorithm (Berger 1997) was used to find the QT interval for each beat using the time-stretch model. The heart rate time series were sampled at 4 Hz. The data were then detrended by using the best-fit line prior to the computation of spectral analyses. The heart rate time series (256 seconds of supine data at 4 Hz =1024 points) was subjected to spectral analyses, and the power spectrum was computed with the Blackman Tukey method (Berger et al 1989). The powers were integrated in the bands of VLF, LF and HF regions.
Results: There were no significant condition differences on ANOVA for the comparison of mean(SD) for HR and QT mean and variability measures. There was a significant caffeine by sleep stage interaction for LF/HF ratios ($F=4.0$; $df=2,18$; $p=0.04$). LF/HF ratios were significantly higher during REM following caffeine administration. There was also a significant caffeine by sleep stage interaction for Qtvi ($F=5.6$; $df=2,12$; $p=0.02$). QTvi was also significantly higher during REM following caffeine administration.
Conclusion: Increased sympathetic activity, as found here for LF/HF ratios and Qtvi in REM would be expected after administration of caffeine, a well-known sympathetic agent. It is possible that significant differences were not found in the wake measure because the time placement of that measure was about 30 min after caffeine administration (pill form) and perhaps before significant drug became available. However, stage 2 and REM observations were chosen to occur at similar times during the second half of the night, so lack of significant findings during stage 2 cannot be explained by caffeine time course.

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Effects Of Zolpidem On Subjective Evaluation Of Sleep And Daytime Alertness And On Psychomotor And Physical Performance Tests In Healthy Volunteers

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Introduction: It is well known that physical activity or athletic ability cannot be exhibited to full extent when the subject had a sleep disturbance or insufficient sleep at night on the day before. In the past, it has been practiced to use hypnotics to overcome sleep disturbances at night before sports event for the athletes, while there has been problem of carryover effect of the medication to the next day. Zolpidem is a medication with the shortest half-life period among the hypnotics now available, and it is known that it has almost no affinity to BZ2 receptor, which causes muscle relaxant effect. In the present study, we administered zolpidem to healthy students and investigated psychomotor function and physical performance of the subjects on the next day.
Methods: The subjects enrolled in the study included 8 healthy male university students. From each subject, the informed consent on the participation in the study was obtained. Zolpidem or placebo was given to

each subject in two sessions over two nights (with one-week wash-out period between the nights). The hypnotic was given immediately before going to bed (23:00), and the subjects were instructed to get up at 7:00 in the next morning. To investigate the remaining effect of the medication on the next day, objective evaluation was carried out at 9:00, 13:00 and 17:00 respectively. For subjective evaluation, self-evaluation was performed at the time of getting up in the next morning and every hour from 7:00 to 22:00. The objective evaluation included combined test, simple discriminatory reaction test, critical flicker fusion (CFF) test, sargent jump (SJ), and 50-meter running test (RT). Subjective evaluation included questionnaire on sleep on the next morning, Stanford Sleepiness Scale (SSS) on the next day, and visual analogue scale (VAS) for recording alertness and fatigue.

Results: In CFF test (time point: 9:00 and 13:00) among the objective evaluation, the results were significantly better in the group, to which zolpidem was given (zolpidem group) ($p = 0.03$). In the subjective evaluation, mean sleep latency was about 30 minutes shorter in zolpidem group compared with placebo group ($p = 0.04$). Mean total sleeping time was about 50 minutes longer in zolpidem group. On the other points, there was no significant difference between zolpidem group and placebo group.

Conclusion: Among the tests performed in the objective evaluation, zolpidem group showed significantly better results in CFF test. In CFF test performed in the previous reports, in which medications such as antianxiety agent of benzodiazepines were given during daytime, it has been reported that the results in the medication group were lower than or equal to those of control group. However, in our present study, the medication at night on the previous day showed rather better results. The causes for such results should be investigated in further experiments. In the subjective evaluation, significant difference was noted only in the reduction of sleep latency and extension of total sleeping time. Sleep latency was reduced to about 1/3, and total sleeping time also showed increase. These findings were supported by the experiments using overnight polysomnography for healthy adults. There have been two reports, which described the use of hypnotics to athletes. Tafti et al. used zopiclone (7.5 mg) in psychomotor function and physical performance similar to our present study. They report that there was no significant difference between zopiclone group and placebo group. It is known that benzodiazepines have effects to cause muscle weakness or memory disturbance, and this may result in the decrease of physical performance. Zolpidem has high affinity only to BZ1 receptor and has only weak muscle relaxant effect. In addition, its half-life period is short. This may have been the reason why there was no carryover effect already before the test on the next day.

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An Open-Label Assessment of Modafinil on Attention and Fatigue in Adolescent and Adult AD(H)D Subjects

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Introduction: Some late adolescent and adult AD(H)D patients decline use of psychostimulants because of side effects, lack of response or stigma associated with using a controlled substance. Modafinil, a class IV alerting agent found to be effective in treating symptoms of narcolepsy or fatigue associated with sleep deprivation, multiple sclerosis and Parkinson's disease, has no known habituation risk and a reasonably benign side effect profile. We have recently attempted modafinil therapy in selected adolescent and adult patients who met rigid DSM-IV behavioral/cognitive criteria for AD(H)D in each associated with subjective description of fatigue quantified on the Fatigue Assessment Instrument (FAI). Mood/personality assessed by Minnesota Multiphasic Personality Inventory (MMPI).

Methods: Retrospective chart analysis of 2 adolescent, 6 adult patients (4 male, 4 female, mean age 42 years, range 17-62) with AD(H)D treated with modafinil 100 to 400 mg per day for more than one month (mean 7 months) to assess effects on attention and fatigue using pre- & post-treatment neuropsychological measures of attention: Test of Variables of Attention (TOVA), Conners' Continuous Performance Test (CPT), Wisconsin Card Sorting Test (WCST), Letter Cancellation Test (LCT) and FAI and sleep log. Concomitant medications were continued.

Results: Normalized cognition on one or more neuropsychological measure - 7 of 8; improved fatigue score (>10%) - 7 of 8; impaired sleep pattern - 0 of 8. Activated anxiety, depression, obsessiveness - 0 of 8.

Conclusion: Modafinil was associated in the majority of patients with improvement in attention and fatigue without significant side effects including none on nocturnal rest. There was no activation of anxiety, obsessiveness or induction of tics as sometimes is the case with conventional psychostimulants. A prospective study of modafinil in adult and adolescent AD(H)D subjects is warranted.

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The Effect of Multiple Doses of Ramelteon (TAK-375) on the Single-Dose Pharmacokinetic Profile of Midazolam in Healthy Adult Subjects

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Introduction: Midazolam is extensively metabolized to 1-OH-midazolam, and this biotransformation predominantly occurs via CYP3A4. Midazolam is, therefore, an important marker substrate to investigate CYP3A4-inhibitory and -inducing properties of a test drug. Ramelteon is a novel selective ML1 receptor agonist being investigated for the treatment of insomnia. This study evaluated the effects of multiple doses of ramelteon on the systemic exposure of midazolam.

Methods: This was an open-label study with 1 sequence of treatment administration. Twenty-eight healthy adult subjects (16 male, 12 female; mean age, 34.8 years) received a single oral 10-mg dose of midazolam with a 2-day washout period, followed by oral ramelteon 32 mg once daily for 9 days, followed by midazolam 10 mg coadministered with ramelteon 32 mg on Day 13. Each dose was given at approximately 8:00AM; subjects fasted overnight prior to pharmacokinetic sampling. Blood and urine samples for pharmacokinetic analysis were collected over 48 hours after each midazolam dosing.

Results: Compared to midazolam administered alone, 32 mg/d of ramelteon given for 9 days had no effect on the midazolam AUC0-inf (geometric mean: 126 [midazolam alone] vs. 119 ngh/mL [plus ramelteon]; 90% CI: 86.5,104) or its Cmax (geometric mean: 45.3 [midazolam alone] vs. 41.8 ng/mL [plus ramelteon]; 90% CI: 82.5, 103). Ramelteon also had no effect on the AUC0-inf for 1-hydroxymidazolam (geometric mean: 55.2 [midazolam alone] vs. 54.1 ngh/mL [plus ramelteon]; 90% CI: 89.4, 107) or its Cmax (geometric mean: 22.4 [midazolam alone] vs. 21.2 ng/mL [plus ramelteon]; 90% CI: 81.3, 110). The incidence of adverse events was higher during administration of ramelteon alone (78.6%) compared to midazolam alone (25.0%) and coadministration of ramelteon and midazolam (25.0%). However, this finding was not considered representative since the number of subjects was not large enough for a meaningful safety assessment and ramelteon was administered for 9 days and midazolam for only 1 day. All but one adverse events were mild in severity (one event was moderate in severity); the most frequently reported adverse event in ramelteon subjects was somnolence (50.0%).

Conclusion: Multiple doses of ramelteon did not influence the single-dose systemic exposure of midazolam indicating that ramelteon is neither an important inhibitor nor an inducer of the CYP3A4 isozyme.

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Effects of Multiple Doses of Fluoxetine on the Systemic Exposure of a Single Dose of Ramelteon (TAK-375) in Healthy Adults

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Introduction: Ramelteon is a novel selective ML1 receptor agonist being studied for the treatment of insomnia. In this study, we examined the effects of fluoxetine (a widely used SSRI that is a CYP 2D6 substrate) on the systemic exposure of ramelteon in healthy adults.
Methods: Twenty-eight subjects (19 male, 9 female; mean age, 30.9 years) received ramelteon 16 mg on Day 1, fluoxetine 40 mg on Days 3-12, and ramelteon 16 mg and fluoxetine 40 mg on Day 13. Pharmacokinetic samples were collected after administration of ramelteon alone and in combination with fluoxetine.
Results: Compared to ramelteon alone, multiple doses of fluoxetine produced significant increases in the systemic exposure of ramelteon (AUC0-inf: 4.66 [alone] vs. 7.00 ngh/mL [plus fluoxetine]; 90% CI: 127, 177) and its peak concentration (Cmax: 3.85 [alone] vs. 5.38 ng/mL [plus fluoxetine]; 90% CI: 118, 166). Similarly, coadministration of fluoxetine increased systemic exposure of M-II, ramelteon's active metabolite (AUC0-inf: 326 [alone] vs. 495 ngh/mL [plus fluoxetine], 90% CI: 143, 161; Cmax: 116 [alone] vs. 136 ng/mL [plus fluoxetine]; 90% CI: 108, 126). Overall, 13 subjects reported a total of 35 adverse events (AEs): 17.9% of subjects experienced 8 AEs with ramelteon alone, 35.7% of subjects experienced 21 AEs with fluoxetine alone, and 18.5% of subjects experienced 6 AEs with combined fluoxetine and ramelteon. The most frequent AEs were somnolence and dizziness. All adverse events (AEs) were considered mild in severity.
Conclusion: Multiple doses of fluoxetine increased the systemic exposure of ramelteon by ~50%. However, this is not considered clinically important because of ramelteon's high inter-individual variability (CV for AUC> 100%) and wide therapeutic window. No dosage adjustment of ramelteon is required when taken with fluoxetine.

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Two-Period Crossover Study to Assess the Drug Interaction Between Ramelteon (TAK-375) and Theophylline in Healthy Adults

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Introduction: Ramelteon is a novel selective ML1 receptor agonist being studied for the treatment of insomnia. Theophylline (THEO) is an important substrate of CYP1A2. In this study, we examined the effects of multiple doses of ramelteon on the systemic exposure of THEO, as well as the effect of THEO on the systemic exposure of ramelteon and its metabolites M-I, M-II, M-III, and M-IV.
Methods: Thirty-six healthy adults (20 males, 16 females; mean age, 32.2 years) underwent two 10-day dosing periods separated by a 5-day washout period. Eighteen subjects received either ramelteon 32 mg/d or the combination of ramelteon 32 mg/d and THEO 300 mg/d and 18 subjects received THEO 300 mg/d or the combination of ramelteon 32 mg/d and THEO 300 mg/d. On the final day of each dosing period, pharmacokinetic samples were collected over 72 hours. All doses were given at approximately 8:00AM; subjects fasted overnight prior to pharmacokinetic sampling.
Results: Compared to THEO alone, multiple doses of ramelteon had no effect on THEO area under the plasma curve (LS mean AUC0-τ: 119 [THEO alone] vs. 121 μgh/mL [plus ramelteon]; 90% CI: 98.3, 106) or its peak concentration (LS mean Cmax: 7.60 [THEO alone] vs. 7.51 μg/mL [plus ramelteon]; 90% CI: 94.0, 104). The presence of THEO increased ramelteon systemic exposure (LS mean AUC0-τ: 22.2 [ramelteon alone] vs. 31.1 ngh/mL [plus THEO]; 90% CI: 123, 160) and its peak concentration (LS mean Cmax: 18.4 [ramelteon alone] vs. 25.0 ng/mL [plus THEO]; 90% CI: 108, 170). Systemic exposure of M-II (an active metabolite of ramelteon) was unaffected by the presence of THEO. The percentage of adverse events considered possibly or probably related to study drug was 72.2% for ramelteon alone vs. 66.7% for combined treatment and 66.7% for THEO alone vs 87.5% for combined treatment. The most common adverse events associated with ramelteon were somnolence, fatigue, and headache. The most common adverse events for THEO were nausea, dizziness, headache, and insomnia. All adverse events were mild or moderate in severity.
Conclusion: Based on the 90% CIs for steady state AUC0-τ and Cmax, multiple doses of ramelteon did not influence the systemic exposure of THEO. Multiple doses of THEO increased the systemic exposure of ramelteon. However, due to the extensive first-pass metabolism of ramelteon, its plasma concentrations are highly variable (intersubject CV in AUC~100%), it has a wide therapeutic window, and its dose/effect relationship is flat. Therefore, the 40% increase in exposure with THEO is not considered clinically important, and no dosage adjustment is required when the drugs are taken together. The present study showed that ramelteon did not substantially inhibit the metabolism of THEO and vice versa.

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Low Dose Mirtazapine Increases Genioglossus Activity in the Anesthetized Rat

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Introduction: Mirtazapine (MIRT) is an antidepressant with multiple actions including (Action-1) an increase in serotonin (5HT) and norepinephrine (NE),(Action-2) blockade of 5HT type 2 receptors, (Action-3) blockade of 5HT type 3 receptors. Serotonin directly applied to the hypoglossal nuclei augments genioglossus activity via 5HT2 receptors. Norepinephrine also augments genioglossus activity. Systemic administration of an 5HT3 receptor blocker has been shown to augment hypoglossal activity. Therefore, Action-1 and Action-3 of MIRT should increase genioglossus activity while Action-2 should decrease GG activity. However, the effect of MIRT on genioglossus (GG) activity at different doses is not known.
Methods: We administered MIRT 0.5 mg/kg, MIRT 5.0 mg/kg, or saline control IP to male Sprague-Dawley rats (N=10 in each of 3 groups) who had undergone urethane anesthesia (1.2 gm/kg) followed by tracheostomy and vagotomy. The rats spontaneously breathed a mixture of air and oxygen. We measured GG and diaphragm EMG activity with fine wire electrodes. The moving time average EMG activity, blood pressure (femoral arterial line), heart rate, and respiratory rate were determined at baseline (post-vagotomy after values stabilized) and every 10 minutes for 3 hours following drug/saline injection. The values for each hour were averaged and expressed as a percentage of the average baseline value.
Results: Peak GG activity: At hour 1: (control) 64.9±6.3%, (MIRT .5) 78.0±4.1%, (MIRT 5) 33.5±5.4% (MIRT 5 < control, $P < 0.05$) At hour 2: (control) 59.9±6.7%, (MIRT .5) 81.9±5.8%, (MIRT 5) 37.9±4.4%. (MIRT .5 > control and MIRT 5 < control, $P < 0.05$). At hour 3: (control) 57.8±7.1%, (MIRT .5) 86.6±5.3%, (MIRT 5) 50.6±7.6%. (MIRT 0.5 > control, $P < 0.05$). Peak diaphragm activity was slightly lower on MIRT

0.5 and MIRT 5 than control (P <0.05). There was no significant differences in respiratory rate or heart rate between control and MIRT. Systolic blood pressure was slightly but significantly lower on MIRT 5 but not MIRT 0.5 than control.
Conclusion: At MIRT 0.5 mg/kg the Genioglossus peak was greater than control at hours 2 and 3. At MIRT 5.0 mg/kg the Genioglossus peak was less than control at hours 1 and 2. We hypothesize that at lower drug concentrations Action-1 and Action-3 of mirtazapine predominated. At higher drug concentrations Action-2 (5HT2 blockade) predominated. At a dose of mirtazapine similar to one used clinically, mirtazapine augments genioglossus activity in the anesthetized rat.

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Pregabalin Dosed BID Efficaciously Improves Self-Reported Sleep Outcomes In Patients With Postherpetic Neuralgia: Report Of A Large, Randomized, Placebo-Controlled Trial

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Introduction: Sleep disturbance is commonly comorbid with neuropathic pain syndromes, including postherpetic neuralgia (PHN). This study evaluated the efficacy of pregabalin-a novel $\alpha 2$–δ ligand with potent analgesic, anxiolytic, and antiepileptic effects-given BID (150, 300, or 300/600 mg/d) for the relief of pain in patients with PHN studied in a 13-week randomized clinical trial. Assessment of patient-reported sleep outcomes by the sleep interference diary and by the Medical Outcomes Study–Sleep (MOS-Sleep) Scale was also included, the results of which are reported here.
Methods: 368 PHN patients with moderate to severe neuropathic pain for ≥3 months receiving at least 1 dose of pregabalin in this multicenter, 13-week, randomized, double-blind, placebo-controlled study were included in this analysis. Patients were assigned to receive placebo (n=93) or pregabalin 150 mg/d (n=87), 300 mg/d (n=98), or 300/600 mg/d (n=90). On awakening each morning, patients rated, on an 11-point scale, how their pain had interfered with their sleep the previous night. Changes in sleep interference were measured by endpoint mean sleep interference score, weekly sleep interference score, and also assessed by the MOS-Sleep Scale. The MOS-Sleep Scale is a patient-rated questionnaire consisting of 12 items that assess the key constructs of sleep. The instrument consists of 7 subscales: Sleep Disturbance, Snoring, Awaken Short of Breath or With Headache, Quantity of Sleep, Optimal Sleep, Sleep Adequacy, and Somnolence, as well as a 9-item Overall Sleep Problem Index. Patients completed the questionnaire at randomization and at study termination.
Results: Comparison of mean sleep interference scores at endpoint and weekly for Weeks 1–13 showed significant improvement for patients who received pregabalin (all dosages) vs placebo (endpoint, P<0.001; weekly P<0.01). All 3 pregabalin groups also showed greater improvement than placebo in mean MOS-Sleep Scale scores for Sleep Disturbance (P<0.002) and the Overall Sleep Problem Index (P<0.003). In addition, the 300/600 mg/day pregabalin treatment group was significantly more favorable than placebo for the Quantity of Sleep domain (P=0.0033). No significant difference from placebo was seen for any pregabalin treatment group for the other subscales.
Conclusion: Each of the 3 BID dosages of pregabalin (150, 300, 300/600 mg/d) administered to this cohort of PHN patients was associated with improved patient-reported sleep outcomes in both patients' daily sleep interference diaries and as measured by the Sleep Disturbance subscale and the Overall Sleep Problem Index of the MOS-Sleep Scale. Beneficial effects on sleep interference began by Week 1 and were sustained throughout the study's 13 weeks. These results confirm and extend those reported in 2001 from a trial of 8-weeks' duration showing that pregabalin significantly improved self-reported sleep outcomes in patients with PHN.

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Dose and Time Dependent Discrimination of Daytime Sleepiness Measured by Multiple Sleep Latency Test (MSLT), Psychomotor Performance Tests (PPT), and Stanford Sleepiness Scale (SSS) after a Single AM Administration of a Sedative Hypnotic Drug

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Introduction: MSLT, PPT, and SSS index the physiological, manifest, and introspective factors of sleepiness. Assessing these tests at peak drug effect after nighttime administration is confounded by the subjects' natural circadian drowsiness. MSLT, PPT, and SSS tests were performed to understand the dose and time dependent influence of a sedative hypnotic drug, zolpidem (Z), after AM administration in well-rested healthy volunteers.
Methods: Sixteen healthy male volunteers (ages 21 to 44) with no history of insomnia participated in this crossover study that evaluated the influence of placebo (P), zolpidem 5 mg (Z5), and zolpidem 10 mg (Z10) after oral AM administration on MSLT, PPT & SSS. Treatments were administered in a fasted state every 2 days in a sleep laboratory. For the week preceding dosing, subjects spent 9 hrs in bed each night. Prior to randomization, the subjects received a baseline MSLT and actigraphy and had to qualify with a sleep latency of >9 minutes (min) and a sleep efficiency between 85 and 95%. Psychomotor performance tests consisted of a battery of computerized tests including simple reaction time (SRT), choice reaction time (CRT), choice reaction accuracy (CRA), digit vigilance time (DVT), digit vigilance accuracy (DVA), and digit vigilance false alarm (DVFA).
Results: Dose and time dependent discrimination was observed when Z5 and Z10 treatments were compared to P and to each other. A significant reduction in sleep latency on the first four tests was found with Z5 and Z10. The mean of the sleep latencies for the first four MSLT evaluations after dosing was 15.9, 9.8 and 6.1 min for the P, Z5, and Z10 treatments, respectively. SRT performance was altered by Z. Performance was reduced by both Z5 and Z10 through 1.5 hrs, whereas Z10's reduction persisted through 2.5 hrs. Both Z5 and Z10 produced statistically significant impairment in CRT and DVA through 1.5 hrs when compared to P and through 3.5 hrs for Z10. DVT significantly differentiated Z5 and Z10 from placebo and Z10 from Z5 for up to 2.5 hrs, whereas the discrimination persisted until 4.5 hrs for Z10 vs. P. SSS scores were statistically higher for Z10 compared to P through 6 hrs after dosing but only through the first 3 hrs for Z5.
Conclusion: In well-rested healthy volunteers, AM administration of zolpidem produced sedation as demonstrated by changes in physiological, manifest, and introspective measures of daytime sleepiness. MSLT, PPT, and SSS can discriminate with respect to dose and time. This capability peaks earlier for the PPT, followed by the MSLT, and persists for the longest with the SSS.

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Valerian as a Hypnotic in Parkinsons Disease: Preliminary Open Label Results with Sleep Logs

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Introduction: Valerian is a botanical with world-wide use as a hypnotic that has undergone several controlled clinical trials in non-neurologically impaired insomniac populations with some evidence of efficacy. We report here preliminary data from the Open Label portion of a double-blind, placebo-controlled, randomized clinical trial of valerian for disturbed sleep in Parkinsons Disease (PD)
Methods: Patients were 18 patients diagnosed with PD (X [SD] age = 61.6 [9.5];13 M, 5 W). Prior to entering a 17-night randomized trial, patients kept a sleep log documenting their sleep for varying intervals (range 5 to 7 days). They also completed a 20-item side effects checklist on a daily basis. Subsequent to the double-blind phase of the clinical trial, patients were provided a 7-day supply of valerian (600 mg, Lichtwer, taken HS) and an additional sleep log/checklist, which they were instructed to complete any night they ingested the valerian. The data to be presented represent Baseline/Open Label comparisons for those subjects with at least 3 nights of data from each of these phases. Means for individual subjects for all available nights were computed and Baseline/Open Label comparisons employed paired t-tests.
Results: Baseline/Open Label comparisons were as follows: for Sleep Latency, 21.7 (17.0) mins vs. 15.0 (13.1) mins ($t = 2.18$, $p = .04$); for Total Sleep Time, 339.4 (80.7) mins vs. 379.8 (66.3) mins ($t = 2.35$, $p = .03$); for daily number of side effects, 0.3 vs 0.1 ($t = 2.13$, $p = .04$). Only two patients experienced a higher rate of side effects during Open Label. The most common were: frequent urination ($n = 1$) and diarrhea and sensitivity to light ($n = 1$).
Conclusion: These data are consistent with the hypothesis that valerian may have modest benefits for disturbed sleep in PD without marked adverse effects. A definitive assessment of effects will depend upon randomized, placebo-controlled clinical trials with both self-reported and polysomnographic outcomes.

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Study to Assess Drug Interaction Between Ramelteon (TAK-375) and Dextromethorphan in Healthy Adults

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Introduction: Ramelteon is a novel highly selective ML1 receptor agonist being studied for the treatment of insomnia. In this study, we examined the effects of dextromethorphan (DM, a CYP2D6 substrate), on the systemic exposure of ramelteon, and vice versa.
Methods: Thirty-six healthy adults (22 males, 14 females; mean age, 34.2 years) were randomized to 1 of 6 treatment sequences, consisting of three 1-day dosing periods separated by two 7-day washout periods. Subjects received 32 mg/d of ramelteon alone, 30 mg/d of DM alone, and ramelteon 32 mg/d coadministered with DM 30 mg/d. Serum and urine pharmacokinetics of ramelteon and its active metabolite, M-II, were assessed after administration of ramelteon alone and in combination with DM. The same analysis was performed for DM and its metabolites, dextrorphan and 3-hydroxymorphinan, after administration of DM alone and in combination with ramelteon. Ratios of the test/reference least square means for AUC0-inf and Cmax, and 90% CI of these ratios, are provided below.
Results: Compared to ramelteon alone, coadministration with DM had no effect on systemic exposure of ramelteon (AUC0-inf: 9.63 [alone] vs. 9.82 ngh/mL [plus DM]; 90% CI: 89.6, 116) or its peak concentration (Cmax: 7.00 [alone] vs. 7.46 ng/mL [plus DM]; 90% CI: 90.1, 126). Similarly, coadministration of DM did not influence M-II systemic exposure (AUC0-inf: 714 [alone] vs. 726 ngh/mL [plus DM]; 90% CI: 98.4, 105) or its peak concentration (Cmax: 214 [alone] vs. 208 ng/mL [plus DM]; 90% CI: 90.4, 104). Compared to DM alone, coadministration with ramelteon had no effect on systemic exposure of DM (AUC0-inf, 10.1 [alone] vs. 11.1 ngh/mL [plus ramelteon]; 90% CI: 101, 120) or its peak concentration (Cmax: 1.35 [alone] vs 1.42 ng/mL [plus ramelteon]; 90% CI: 95.4, 115); systemic exposure of dextrorphan (AUC0-inf: 2047 [alone] vs. 2088 ngh/mL [plus ramelteon]; 90% CI: 99.5, 105) or its peak concentration (Cmax: 328 [alone] vs. 323 ng/mL [plus ramelteon]; 90% CI: 93.2, 104); or systemic exposure of 3-hydroxymorphinan (AUC0-inf: 1134 [alone] vs. 1167 ngh/mL [plus ramelteon]; 90% CI: 100, 105) or its peak concentration (Cmax: 132 [alone] vs. 131 ng/mL [plus ramelteon]; 90% CI: 95.0, 104). The incidence of adverse events (AEs) was 25% for ramelteon alone, 22.9% for ramelteon and DM, and 11.8% for DM alone. The most commonly reported AEs were fatigue, somnolence, and headache. All AEs were mild. Urinary excretion of ramelteon and DM was similar across treatments.
Conclusion: Systemic exposures to ramelteon and its M-II metabolite were unaffected when ramelteon was administered with multiple doses of DM. DM and its 2D6-mediated metabolite dextrorphan and 3A4-mediated metabolite 3-hydroxymorphinan were also unaffected after administration of multiple doses of ramelteon. The present study shows that, on the basis of systemic exposures of drug, ramelteon and DM may be coadministered without adjusting dosage of either drug.

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Modafinil as Potential Treatment for Cocaine Dependence

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Introduction: Cocaine dependence remains a major public health problem. Findings from the 2002 National Survey on Drug Use and Health estimated that 2 million Americans (0.9%) aged 12 or older were current cocaine users. No effective pharmacologic treatment for cocaine dependence has been determined. Ideally, a pharmacologic therapy for cocaine addiction should have limited abuse potential, ameliorate abstinence syndrome, suppress cocaine use, and have a favorable safety and pharmacokinetic profile. The novel wake-promoting agent modafinil selectively modulates hypothalamocortical pathways involved in the regulation of normal wakefulness and has lower discrimination and reinforcing properties than CNS stimulants. Preliminary data indicate that modafinil significantly blunts cocaine euphoria and reverses cocaine withdrawal symptoms within hours. This study evaluated the efficacy and safety/pharmacokinetic profile of modafinil as potential treatment for cocaine dependence.
Methods: A safety/pharmacokinetic interaction study between intravenous (IV) cocaine and steady-state oral modafinil (200 mg twice daily for 7 days followed by 400 mg twice daily for 7 days) was conducted in non–treatment-seeking subjects with cocaine dependence. In double-blind fashion, cocaine (20 mg or 40 mg) or saline was administered intravenously over 1 minute. Modafinil was administered open-label. Subjective visual analog scale (VAS) measures of "any drug effect," "cocaine high," and "amount willing to pay" were assessed, and pharmacokinetic interactions between cocaine and modafinil were determined. Tolerability and safety assessments included blood pressure/heart rate, adverse events, clinical laboratory parameters, and behavioral/psy-

chiatric toxicities.
Results: This study included 12 inpatients (mean[±SD] age=33±10 years). Mean duration of cocaine use was 11±8 years. Modafinil (400 and 800 mg/day) significantly reduced cocaine euphoria as assessed using VAS measures of "any drug effect," "cocaine high," and "amount willing to pay" (p<.017). Modafinil caused no increase in plasma concentrations of cocaine versus baseline and no inhibition of cocaine elimination. Modafinil steady-state caused no increase in systolic/diastolic blood pressure or heart rate (at either dose of modafinil or cocaine). Modafinil (400 and 800 mg/day) significantly reduced peak systolic pressure caused by cocaine (20 or 40 mg IV). The most common adverse events were headache (n=10, 83%), insomnia (n=9, 75%), dyspepsia (n=4, 33%), and nasal congestion (n=4, 33%). Modafinil had no clinically meaningful effects on laboratory parameters and was not associated with behavioral/psychiatric toxicities.
Conclusion: Modafinil showed positive effects in reducing cocaine euphoria, suggesting it may be an effective medication for cocaine dependence. Modafinil was well tolerated when co-administered with cocaine in non–treatment-seeking volunteers with cocaine dependence.

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Clinical Doses Of Morphine Alters Sleep In Healthy Young Adults

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Introduction: One of the leading causes of sleep disturbances in medical illness is pain. Sleep disturbances are reported by 2/3 of patients suffering from a variety of painful disorders. Providing effective analgesia is considered an important intervention to reduce these disturbances. Nevertheless, the effects of opioids on sleep remain ambiguous as previous studies have been conducted mainly with post-addicts. Since morphine and other opioids remain the treatment of choice to relieve moderate to severe pain, it is imperative to understand their effects on sleep. The purpose of this study was to evaluate the effects of acute clinical doses of morphine on sleep in healthy young adults.
Methods: Seven healthy subjects (5F, 2M; mean age = 25 ±1.6 years) showing normal sleep patterns participated in this study consisting of three nights in the sleep laboratory. Subjects were randomly assigned to morphine (IV injections of 1 mg kg-1), placebo (IV injections of 0.9% NaCl), and baseline (untreated) conditions during which standard polysomnographic sleep and respiratory variables were measured. During injection nights, a first bolus injection was given 30-60 minutes before the lights were turned off, and a second one was administered when subjects were asleep at mid-point of the night. The treatment effect was analyzed with ANOVAs using a latin square cross-over design followed, when appropriate, by Tukey's contrasts.
Results: Acute clinical doses of morphine altered sleep architecture significantly causing an important decrease (75%) in slow-wave sleep ($F(2,9) = 19.63$; $p = 0.0005$), though this loss was compensated by a significant increase (15%) in non-REM stage 2 sleep ($F(2,9) = 20.0$; $p = 0.0005$). REM sleep alterations following morphine administration included reductions in REM sleep duration ($F(2,9) = 4.57$; $p = 0.04$), number of REM periods ($F(2,9) = 8.8$; $p = 0.007$), and REM density ($F(2,5) = 25.5$; $p = 0.00001$). Yet, REM sleep duration only decreased by 5%, and the number of REM periods did not differ between morphine and placebo conditions. Although, total sleep time was diminished during morphine condition compared to baseline, the difference between morphine and placebo conditions was in the order of 10 minutes and did not reach statistical significance. Respiratory and other sleep variables such as EEG alpha-delta sleep, number of sleep stage shifts or correlates of arousal (e.g. number of awakenings, total number of arousals) were similar across treatment conditions.
Conclusion: This study reports on the effects of clinical doses of morphine on sleep structure in healthy young adults. Unlike findings observed in post-addicts acute morphine administration does not seem to increase correlates of arousal. Although sleep alterations were observed, morphine appears to affect sleep in ways similar to other types of pain medications (i.e. acetylsalicylic acid, NSAIDs), and sedative/hypnotics. Whether or not morphine presents unique adverse effects on sleep merits further investigation. Nevertheless, as there is increased awareness of an intimate relationship between pain and sleep, it remains essential to provide optimal relief to pain patients which in turn may grant them a good night sleep.

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Does Modafinil Enhance Cognitive Performance In Young Volunteers Who Are Not Sleep-Deprived?

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Introduction: Modafinil is a selective wakefulness-promoting drug, licensed in the UK for EDS in narcolepsy and OSAHS. Whilst it has been shown to maintain cognitive performance at or near baseline level in conditions of sleep deprivation, reports regarding its cognitive-enhancing effects in healthy volunteers have been equivocal. This may have been due to different test orders, length and/or time of testing, as well as the specific tasks used. The aim of the present study was to clarify these issues by investigating effects on cognition in young volunteers who were not sleep-deprived.
Methods: Fifty-nine healthy volunteers (28 men and 31 women, aged 19-22 years) were randomly allocated to placebo, or modafinil (100 or 200 mg) and 2 h later, in the early evening, completed rating scales of 'sleepiness' and 'fatigue', before and after a long (2 1/4 h), extensive battery of cognitive tests. This included several from the Cambridge Neuropsychological Test Automated Battery (CANTAB), as well as some pen and paper tests. They were selected to assess memory (short and long-term), attention, mental flexibility, planning, verbal fluency, reaction time and constructional ability.
Results: There were no significant differences between the three groups in ratings of 'sleepiness' or 'fatigue' before cognitive testing and no treatment-associated changes in these ratings, although all groups felt more sleepy and fatigued after the testing session ($p<0.005$). Significant improvement with modafinil was observed in two tasks with attentional and short-term memory components. In the Digit Span test (forward), the 100 mg group performed significantly better than the placebo group ($p<0.01$). In the Pattern Recognition Memory task, the 200 mg group recognised significantly more patterns than the placebo group ($p<0.05$) and this was accompanied by a slowing of response latency ($p<0.05$). However, the subjects in the 200 mg group were significantly faster in a simple colour naming of dots than those in the placebo group ($p<0.05$). No effects of modafinil were seen in the Spatial Working Memory task or in tests of long-term memory or executive function, suggesting that perhaps modafinil's benefits are limited to easier tasks. This view is also

supported by the finding of significantly better performance by subjects in the 200 mg group compared with those in the placebo group in the Rapid Visual Information Processing test of sustained attention ($p<0.05$), but not in the harder Paced Auditory Serial Addition Task.
Conclusion: The pattern of effects observed in this study could not be related to test order or length of testing session, but testing in the early evening, at the end of a normal working day, when the subjects' speed of response is slower, may have contributed to the effects in the sustained attention task. The limited cognitive effects found are insufficient for modafinil to be considered as a cognitive-enhancer in non sleep-deprived individuals.

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Sleep Modulating Effects Of A Novel Melatonin Derivative (MLTD) In Rats.

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Introduction: Melatonin is an indole-derived neurohormone and has a proven role in the sleep-wake cycle. 2-iodomelatonin is a potent melatonin agonist with highest affinity for melatonin (MT1/MT2) receptors than melatonin. The aim of this study was to evaluate, in comparison with melatonin (MLT), the effects of a novel 2-iodomelatonin derivative 1, having a 2-trifluoromethyl grop (MLTD) on the sleep-wake cycle in freely behaving male Sprague-Dawley rats.
Methods: Male Sprague-Dawley rats were kept in a constant air-conditioned room at 25 ± 1oC with relative humidity 60 ± 6%, and a light cycle of 12:12 (lights on 8:00 h and lights off 20:00 h). The animals were implanted with cortical electroencephalogram (EEG), neck electromyogram (EMG) electrodes and stainless steel cannulae for third cerebroventricular (icv) infusion under deep anaesthesia. EEG and EMG were monitored for three consecutive days during continuous icv saline infusion at a rate of 10 µl/h after the recovery period of 10 days. Doses of MLTD (100, 300 and 500 nmol/100 µl saline) or MLT (500 nmol/100 µl saline) replaced the icv infusion of saline during the diurnal infusion period (7:00-17:00). The vigilance states obtained during saline, MLTD and MLT administration were scored visually as rapid eye movement (REM) sleep, non-REM (NREM)sleep and wakefulness.
Results: The diurnal infusion of MLTD showed that the total sleep duration was significantly increased during the infusion period and wakefulness was suppressed concurrently. 12-h light and 12-dark periods revealed that both doses of 300 and 500 nmol of MLTD significantly($p\leq0.05$) increased NREM sleep during these periods due to increase in the episode duration. REM sleep was only significantly increased during the light period at the dose of 500 nmol. However, MLT only showed non-significant increase in NREM sleep due to significant increase in both episode number and duration only during the light period with no effect during the dark period showing short duration effects. Moreover, in comparison with MLTD, MLT showed no effect on REM sleep during the light period. The 4-h time intervals analysis showed that sleep-wake states were significantly modulated during the second 4-h time intervals. NREM sleep was increased above the baseline value for 100 nmol and significantly increased at doses of 300 and 500 nmol, MLT also increased NREM sleep significantly, however, only 500 nmol of MLTD also increased REM sleep during this period and MLT had no effect on REm sleep. Doses of 300 and 500 nmol (MLTD) and 500 nmol (MLT) significantly increased total sleep during the second 4-h time interval. The results obtained during the third 4-h time interval showed that only the dose of 100 nmol MLTD had significant effects on NREM sleep and total sleep. The results showed time- and dose-dependent effects.
Conclusion: The diurnal icv infusion of MLTD increased NREM and REM sleep and decreased wakefulness. The results obtained showed that MLTD is probably more potent in promoting sleep than MLT and may play an important role in modulating sleep-wake state.

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Tolerance to Hypnotic Effects of Ethanol in Insomniacs

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Introduction: Our previous studies showed that ethanol at low doses improves the sleep of insomniacs and further insomniacs self administer low ethanol doses at bedtime (i.e. as a hypnotic) to a greater extent than do non-insomniacs with similar social drinking histories. However, what may initially be sleep-medicating behavior may begin to demonstrate some of the characteristics of drug-seeking behavior (i.e. alcoholic drinking) as tolerance to the sleep effects develops. This study explored the degree to which tolerance to the hypnotic effects of ethanol develops in insomniacs.
Methods: Twenty-four healthy (50% female-male), 21-55 yrs old, insomniacs in good medical and psychiatric health with no history of alcoholism or drug abuse participated. All had chronic complaints of insomnia and sleep efficiencies <85% on a screening 8-hr NPSG with no evidence of primary sleep disorders. They were randomized to receive 0.0, 0.3, or 0.6 g/kg ethanol before sleep for six consecutive nights. Beverages were consumed over 30 min and drinking was completed 30 min prior to bedtime. Standard 8-hr NPSGs, scheduled according to participants diary-reported sleep habits, were collected each night. The NPSG parameters on night 2 (night 1 was considered an adaptation night) were compared to those of night 6 among the 3 ethanol dose groups by mixed design MANOVAs.
Results: Sleep efficiency showed a dose by night interaction ($F2,21 =5.61$, $p<.01$). With the 0.6 g/kg dose sleep efficiency was improved on night 2 (78.2+/-7.3, 79.6+/-9.3, 86.3+10.3% for 0.0, 0.3 and 0.6 g/kg doses, respectively) relative to placebo ($p<.02$), but was worsened on night 6 vs night 2 ($p<.04$) and no longer differed on night 6 from placebo (79.2+/-8.2, 83.6+/-5.3, 70.6+/-5.3%). Minutes of stage 3-4 sleep similarly showed an interaction ($F2,21 =3.46$, $p<.05$). While the 0.6 g/kg dose was not statistically different ($p<.10$), albeit numerically higher, than placebo on night 2 (45.8+/-9.4, 55.3+/-8.7, 74.2+/-8.8 min), minutes of stage 3-4 declined on night 6 vs night 2 ($p<.04$) for the 0.6 g/kg dose (47.9+/-10.8, 62.9+/-10.0, 51.5+/-10.2 min). Minutes of stage 1 showed a main effect of dose ($F2,21 =3.48$, $p<.05$) with the 0.6 g/kg dose being lower compared to placebo and the 0.3 g/kg dose. Other of the NPSG parameters did not show effects.
Conclusion: These are the first data to show tolerance development to the hypnotic effects of ethanol in insomniacs and further, that the tolerance develops rapidly (i.e.<week). This finding has important implications regarding insomnia and alcohol abuse in that approximately 30% of those from the general population who report using alcohol to aid their sleep report using it longer than one week (see companion abstract). Our laboratory studies have shown that tolerance development is associated with dose escalation.

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The Effects of Tiagabine on the Sleep of Older Adults

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Introduction: Tiagabine, a selective ?-aminobutyric acid (GABA) reuptake inhibitor (SGRI), has been reportred to have sleep-enhancing effects. It produces an increase in extracellular GABA by inhibiting reuptake on the GAT-1 transporter. Absorption of tiagabine is fairly rapid with a tmax of about 45 minutes in the fasting state and an elimination half-life of 7-9 hours in hepatically un-induced patients. The effect of three doses of tiagabine on the sleep of elderly subjects without sleep complaints was assessed in this study.
Methods: Twenty-six subjects (13 male, 13 female) with a mean age of 67.8 years (range 60-80) with reported normal sleep were randomized to receive tiagabine 2mg, 4mg, 8mg (T2, T4, T8, respectively) and placebo (PBO), each on two consecutive nights, according to a Latin-square design. Two-night treatment periods were separated by five nights at home without study medication. All subjects were free of medical and psychiatric disorders, kept a regular sleep schedule, habitually consumed < 10 alcoholic drinks/week and < 400mg caffeine/day, and did not take CNS active medications. A standard PSG adapted subjects to laboratory procedures and excluded those with sleep disorders. Morning procedures included a post sleep questionnaire, DSST, Karolinska Sleepiness Scale, and Immediate and Delayed Recall Word Test. Because the primary purpose of the study was to identify a dose to be tested in patients populations, statistical comparisons of interest involved each tiagabine dose versus PBO.
Results: Twenty-four of 26 subjects completed the study. One subject was terminated because of noncompliance and another because of unsteady gait the morning following the first dose of 8mg. T2 did not differ from PBO on any variables. T4 had a significantly greater amount of TST (407.7 min) than PBO (396.0 min; p=0.022) and less WASO (64.9 min) compared to PBO (77.2 min; p=0.019). Minutes of SWS increased for T4 (59.7) relative to PBO (44.5; p=0.015). There also was a trend for less Stage 1 (73.9 min) with T4 compared to PBO (81.3 min; p=0.059). T8 showed a trend toward increased TST (p=0.073), but no difference for WASO. REM latency was longer for T8 (94.2 min) than PBO (71.8 min; p=0.001). Compared with PBO, T8 also showed significantly more SWS (87.0 vs 60.0 min; p<0.0001), less Stage 1 (62.4 vs 81.3 min; p<0.0001) and less REM (58.4 vs 68.3 min; p=0.001). There were no group differences on subjective sleep measures or measures of morning sedation.
Conclusion: This exploratory study in healthy older adults suggests that tiagabine 4 and 8mg have positive effects on sleep, particularly sleep maintenance variables, with infrequent adverse effects. Further research with tiagabine at dosages of 8mg or less appears warranted in elderly clinical populations.

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Codeine, Pain Threshold, and Midday Sleepiness

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Introduction: Circadian variations in drug effects are well documented, including analgesic effects. A biphasic circadian rhythm to sleepiness-alertness is also known with the primary peak in sleepiness occurring at night and the secondary peak over the midday. Sleepiness is known to blunt a number of physiological processes and it also may have a partial role in the circadian variation of analgesic effects. This study evaluated pain threshold in healthy normals in the morning and midday to determine whether the analgesic effect of codeine is blunted as a function of time-of-day (TOD)
Methods: Six healthy, normal adults, 21-35 yrs old, participated. All were in good medical and psychiatric health with no history of alcoholism or drug abuse. All had sleep efficiencies >85% on a screening 8-hr NPSG with no evidence of primary sleep disorders and an average sleep latency of >8 min on a standard MSLT conducted on the following day. Each underwent four conditions presented in a Latin Square design: 8 hrs time-in-bed (TIB) + placebo, 8 hrs TIB + codeine 60 mg bid, 4 hrs TIB + placebo, and 0 hrs TIB + placebo. In the 8 hrs TIB conditions bedtime was set to 2300-0700 hrs and this report only includes the data of the 8 hrs TIB codeine and placebo conditions. The following day after arising at 0700 hrs and a breakfast (0800-0830 hrs) each participant received codeine 60 mg or placebo at 0900 and 1300 hrs. A standard MSLT was conducted at 1000, 1200, 1400, and 1600 hrs. Pain threshold assessments were done at 1030 and 1430 hrs using a novel radiant heat stimulation method. At each assessment finger withdrawal latency (sec) was measured for 5 randomly presented intensities of radiant heat directed to the index finger pad.
Results: Sleep latency on the MSLT was higher on the am (mean 1000 and 1200 hrs) tests vs pm (1400 and 1600 hrs) tests ($F_{1,6}$ =10.75, p<.02; main effect of TOD) across placebo (13.1+3.1 vs 11.8+3.0 min) and active drug (8.9+/-4.3 vs 4.6+/-2.5 min). Mean finger withdrawal latency on the am and pm testing after placebo was 12.6+/-4.5 and 10.9+/-4.9 sec and after codeine it was 14.0+/-5.4 and 13.7+/-6.0 sec. Finger withdrawal latency was reduced on the pm testing relative to the am testing ($F_{1,6}$ =9.58, p<.02; main effect of TOD) and was increased with codeine vs placebo ($F_{1,6}$ =5.81, p<.05; main effect of drug). The change in finger withdrawal latency with drug on the am vs pm testing (i.e., drug minus placebo - greater positive scores reflecting greater analgesia) was 1.42+/-2.7 vs 2.79+/-2.2 sec. There was no interaction of TOD by drug effects. As the change scores reflect, rather than blunting the analgesic effect of codeine, they were numerically, although not significantly, greater on the pm testing.
Conclusion: The results of this study indicate that sleepiness over the midday is associated with hyperalagesia (i.e., reduced pain threshold). Further, while codeine increases pain threshold (i.e., is analgesic) there is no blunting of its analgesic effects as a function of TOD, and even, possibly an enhancement.

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Effects of Fluconazole and Ketoconazole on the Pharmacokinetics of Ramelteon (TAK-375) in Normal Healthy Male and Female Subjects

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Introduction: FLU and KET are important inhibitors of CYP2C9 and CYP3A4, respectively. Ramelteon is a novel selective ML1 receptor agonist being studied for the treatment of insomnia. This study describes the systemic exposures of ramelteon and its major metabolite, M-II, when a single dose of ramelteon is coadministered with multiple doses of fluconazole (FLU) or ketoconazole (KET).
Methods: For each of the two studies, 28 subjects were randomized into

two 4-day dosing periods separated by a 14-day washout period. In one study, subjects received either a single dose of ramelteon 16 mg on Day 4 or FLU 400 mg on Day 1 and 200 mg QD on Days 2-4 plus ramelteon 16 mg on Day 4. In another study, subjects received either a single dose of ramelteon 16 mg on Day 4 or KET 200 mg BID on Days 1-4 plus ramelteon 16 mg on Day 4. After each dose of ramelteon, pharmacokinetic samples were collected over 24 hours.
Results: Compared to ramelteon alone, the combined treatments with FLU and with KET significantly increased AUC0-inf of unchanged ramelteon (5.05 [alone] vs. 12.7 ngh/mL [plus FLU], 90% CI: 215, 295; 6.89 [alone] vs. 12.7 ngh/mL [plus KET], 90% CI: 157, 216). Cmax of ramelteon was significantly increased with the combined treatments (4.33 [alone] vs. 10.6 ng/mL [plus FLU], 90% CI: 193, 308; 5.75 [alone] vs. 7.81 ng/mL [plus KET], 90% CI: 110, 168). Tmax of ramelteon was delayed in the presence of FLU (0.70 vs. 0.75 h; P=0.5717) and KET (0.69 vs. 1.02 h; P=0.0047). The half-life (T1/2) of ramelteon was slightly longer with the combined treatments (1.10 [alone] vs. 1.46 h [plus FLU]; 1.34 [alone] vs. 1.79 h [plus KET]). For M-II (the active metabolite of ramelteon), AUC0-inf (P<0.001), Cmax (P<0.001), and T1/2 increased when ramelteon was coadministered with FLU and KET. M-II Tmax was significantly delayed with coadministration of FLU (P<0.0098) and KET (P<0.001). Urinary excretion of ramelteon and its metabolites was negligible for all treatment groups. The incidence of adverse events was greater during coadministration of FLU (92.0%) than with ramelteon alone (74.1%) and during coadministration of KET (96.4%) than with ramelteon alone (66.7%), with fatigue being the most commonly reported adverse event. Most adverse events were mild, and none was severe.
Conclusion: FLU and KET both significantly increased the systemic exposures (AUC0-inf) of ramelteon. However, these increases of 152% with FLU and 84% with KET, though moderate, were not considered substantial in view of the fact that ramelteon undergoes extensive first-pass metabolism, it has highly variable plasma concentrations [intersubject CV in AUC~100%], and it has a flat dose/effect relationship. These results suggest that neither CYP3A4 nor CYP2C9 is the predominant isozyme involved in the extensive metabolism of ramelteon.

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A Phase I Study to Investigate the Absolute Bioavailability of a Single Oral Dose of Ramelteon (TAK-375) in Healthy Male Subjects
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Introduction: Ramelteon is a novel selective ML1 receptor agonist being studied for the treatment of insomnia. The present study was conducted in healthy male subjects to determine the absolute bioavailability of orally administered ramelteon.
Methods: Eighteen healthy male subjects (age range, 19 to 40 years) were randomized to receive ramelteon either as a single 16-mg oral dose or a 5-minute, 2-mg IV infusion. Subjects were treated with the alternative route after a washout period of at least 1 week. Serum samples for the pharmacokinetic analysis of ramelteon and its metabolites (M-I, M-II, M-III, and M-IV) were collected over 24 hours following each ramelteon administration. The absolute bioavailability of ramelteon was based on the geometric LS mean ratio for AUC0-inf(norm) between the tablet and IV formulation.
Results: The absolute bioavailability of ramelteon following oral dosing was very low (<2%). For individual subjects, the absolute bioavailability was variable, ranging from 0.5% to 12%. After reaching Cmax, serum levels declined in a monophasic manner, with a short elimination half-life of approximately 1 hour. The incidence of adverse events following oral and IV infusion were similar, with somnolence and fatigue accounting for the majority of adverse events. A previous study with radiolabeled ramelteon showed that as much as 84% of the orally administered radioactivity was recovered in the urine, mostly as several metabolites, with unmetabolized ramelteon accounting for <0.1% of the administered dose.
Conclusion: These findings indicate that the oral absorption of ramelteon is excellent, and the drug undergoes extensive first-pass metabolism.

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A Phase-I Open-Label Study of the Absorption, Metabolism, and Excretion of (14C)-Ramelteon (TAK-375) Following a Single Oral Dose in Healthy Male Subjects
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Introduction: Ramelteon is a novel selective ML1 receptor agonist being studied for the treatment of insomnia. This study evaluated the pharmacokinetics, metabolism, and excretion of ramelteon.
Methods: Six healthy male subjects received a single oral dose of 16 mg (14C)-ramelteon following an overnight fast. Blood, urine, and fecal samples were collected for analysis.
Results: Ramelteon was rapidly absorbed, with a Tmax of 0.3 hours, and rapidly eliminated, with a half-life of 1.2 hours. Similarly, the metabolites were rapidly formed and eliminated, with half-lives of 1 to 3 hours. Systemic exposure of the active metabolite M-II was 20- to 30-fold greater than that of ramelteon, while the exposures of M-I, M-III, and M-IV were one- to four-fold higher than that of ramelteon. Of the total radioactivity administered, 84% was eliminated in the urine, and 4% was eliminated in the feces, with metabolites of ramelteon accounting for the majority of the dose eliminated. High urinary recovery of radioactivity indicates that there was at least 84% oral absorption of ramelteon. Negligible excretion of ramelteon in the urine and low serum concentrations of ramelteon (relative to metabolites) within 15 minutes of oral dosing indicate that ramelteon undergoes extensive first-pass metabolism. Ramelteon was metabolized primarily via oxidation to hydroxyl and carbonyl groups, with secondary metabolism to form glucuronide conjugates. All adverse events considered to be possibly related to the study drug were mild in intensity, with the exception of one event of headache, which was moderate in intensity. Seven of the 11 drug-related events were reported by a single individual, and three of the six subjects did not report any drug-related adverse event.
Conclusion: Ramelteon is rapidly absorbed and undergoes extensive first-pass metabolism.

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Sleep Architecture Changes During Marijuana Withdrawal
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Introduction: Sleep difficulty and strange dreams are among the most commonly reported symptoms of marijuana withdrawal. However, few polysomnographic studies of marijuana withdrawal have been conducted in the past 20 years. The goal of the present study was to identify changes in sleep architecture during the first 3 days of abstinence in dependent heavy users of marijuana.

Methods: Three marijuana-dependent males (mean age 40 years) with an average lifetime use equivalent to thrice daily for 18.8 years completed five consecutive nights in a sleep laboratory. Bed and wake times were calculated from sleep diaries (mean bedtime 10:55 pm; mean time in bed 7 hr 35 min). Subjects maintained their usual marijuana use pattern until they entered the laboratory on the second night. The first night was an acclimation night; the second served as a pre-abstinence comparison. Subjects abstained from marijuana use (verified by daily urinalysis) for the next three days. Standard polysomnography techniques were used, and marijuana withdrawal symptoms were measured with visual analog scales.
Results: REM percent of total sleep time was significantly increased on day 1 of abstinence, and REM latency was significantly decreased on day 2 of abstinence ($p < 0.05$; paired t-test). Although group means of other variables were comparable across the abstinence period, peak effect analyses revealed that the directionality of many changes was identical across subjects. Specifically, there were decreases in sleep efficiency (mean -9%) and REM latency (mean -77 min), as well as increases in marijuana craving (mean +24 on a 100-point scale), irritability (mean +16 on a 100-point scale), REM percent of total sleep time (mean +5.9%) and slow wave percent of total sleep time (mean +6.9%) in each subject at some point during the abstinence period.
Conclusion: Abstinence from marijuana in chronic users is characterized by robust sleep abnormalities that are robust but vary in time course across individuals. The extent to which these abnormalities are similar to those seen in depressed individuals is worthy of future study.

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A Randomised Double-Blind Placebo-Controlled 10-Way Cross-Over Study Shows That A New Zolpidem Modified-Release Formulation Improves Sleep Maintenance Compared To Standard Zolpidem

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Introduction: Zolpidem rapidly induces sleep and increases sleep duration with a low incidence of next-day residual effects. A modified-release (MR) zolpidem formulation incorporating both imediate- and prolonged-release preparations has been developed to provide sustained plasma zolpidem concentrations in the middle portion of the night (3-6 hours post-dose) and so improve sleep maintenance while possessing the same elimination half-life as standard zolpidem. To decide which formulation of zolpidem MR provides the optimal duration of sleep maintenance without residual effects, a randomized double-blind placebo- and zolpidem 10 mg-controlled cross-over pharmacodynamic screening of eight zolpidem MR formulations (A-H) providing a range of total zolpidem doses from 7.5 to 15 mg was conducted.
Methods: During ten 1-night polysomnographic (PSG) assessments 36 healthy (mean age 25 +/- 5 years, 44 % female) non-sleep disturbed subjects were dosed with one of the treatment conditions and then exposed to pre-recorded traffic noise at a mean sound level of 52 db (within a dynamic range of 32-77 db) for an 8-hour period. Each assessment period was separated by a 7- to 14-day washout. On the morning following dosing (8 and 9 hours post dose) a battery of psychometric assessments was performed. Sleep was evaluated using manually scored polysomnography and the Leeds Sleep Evaluation Questionnaire was used to assess subject's residual morning-after activity and sleep quality.
Results: 32 subjects completed the study. The traffic-noise model was capable of discriminating between the zolpidem MR treatments. Two particular formulations, including the "E" (12.5 mg), significantly reduced the total night number of awakenings (wakeful events superior or equal to 15 seconds) when compared with placebo ($p = 0.0005$ and $p = 0.0411$, respectively) and for "E" compared with standard zolpidem ($p = 0.0021$). In order to investigate the time course of hypnotic action, awakenings were also analyzed on a per-hour base. All formulations significantly reduced the number of awakenings up to 3 hours after sleep onset. Three formulations, including "E", were effective for 5 hours when compared with placebo. Standard zolpidem and 3 of the MR formulations, including "E", showed no evidence of residual effects in psychometric/cognitive tests but all over formulations showed a difference from placebo on at least one psychometric test. All active treatments were perceived subjectively (LSEQ) as increasing both the ease of getting to sleep and the quality of sleep.
Conclusion: The traffic-noise model allowed the sensitive discrimination of drug effects using PSG assessments by evaluating 8 distinct formulations of MR zolpidem. The "E" (12.5 mg) formulation not only proved to be more effective on sleep maintenance than standard zolpidem but also maintained the low potential of standard zolpidem for residual next-morning effects.

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Evaluation of a Pharmacokinetic Interaction Between Eszopiclone and Digoxin

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Introduction: Eszopiclone (ESZ) is a novel, non-benzodiazepine agent under investigation for the treatment of insomnia. Digoxin is a digitalis glycoside that has effects on the myocardium and is prescribed for congestive heart failure, paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter. Because digoxin has a narrow therapeutic index and is commonly used in the adult population in whom insomnia medications are used, this trial was conducted to study the effect of a single dose of eszopiclone on the pharmacokinetics of digoxin at steady state.
Methods: This was a single-center, in-patient, open-label, daytime dosing study in healthy adult volunteers. A loading dose of digoxin was administered on day 1 (0.5 mg BID, doses separated by 12 hours), followed by once daily dosing of digoxin 0.25 mg on Days 2-7. A single dose of eszopiclone 3 mg was administered along with digoxin on Day 7. On testing Days 6 and 7, drugs were administered in the fasting state (10 hrs after eating). To evaluate the pharmacokinetics of digoxin, blood was drawn pre-dose on Days 4-7 and additionally at 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 6 and 7. The primary endpoint was the comparison of AUC(0-τ), and Cmax of steady state digoxin when administered alone (Day 6) to the combined treatment with eszopiclone (Day 7). If the 90% confidence intervals of the ratios fell within 80-125% for digoxin AUC(0-τ), and Cmax, it would be concluded that eszopiclone did not affect the pharmacokinetics of digoxin.
Results: Twelve subjects (7 male) aged 24-64 years (mean 40.7) were enrolled and completed the study. Steady state digoxin plasma concentrations were achieved on Day 4. On Day 6, steady state digoxin mean Cmax was 2.3 ng/ml, median tmax was 1.0 hr, and mean AUC(0-τ) was 21.2 ng*hr/ml. On Day 7 (concomitant eszopiclone administration) the digoxin mean Cmax was 2.1 ng/ml, median tmax was 1.0 hr, and mean AUC(0-τ) was 21.0 ng*hr/ml. The 90% confidence intervals for AUC(0-τ), and Cmax were within the 80-125% range, demonstrating that the pharmacokinetic profile of steady state digoxin was not affected by a single dose of eszopiclone 3 mg.
Conclusion: A single dose of eszopiclone 3 mg did not affect the steady state pharmacokinetics of digoxin in healthy volunteers.

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Evaluation of Pharmacokinetic and Pharmacodynamic Interactions Between Eszopiclone and Warfarin

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Introduction: Eszopiclone is a novel non-benzodiazepine, cyclopyrrolone agent under development to treat insomnia. Warfarin, a racemic drug, is a widely prescribed anticoagulant indicated for the prophylaxis and treatment of venous thrombosis and thromboembolic complications associated with atrial fibrillation and cardiac valve replacement, and reduction of recurrent myocardial infarction. Warfarin is metabolized via the cytochrome p450 enzyme system (CYP450) and, therefore, has the potential to interact with other drugs metabolized via this pathway. An in vivo pharmacokinetic/pharmacodynamic interaction study was conducted in healthy subjects because warfarin has a narrow therapeutic index and is widely prescribed.
Methods: This was a single-center, in- and outpatient, daytime, randomized, 2-period, 2-treatment crossover, open label study conducted in healthy male and female volunteers. In one treatment period subjects were administered eszopiclone 3 mg daily for 5 days. On the last day of dosing subjects also received a single dose of warfarin 25 mg. In the other treatment period subjects received a single dose of warfarin 25 mg. Treatment periods were separated by a 14-day washout. Subjects were dosed in the fasted state (no food 9 hours prior to and 2 hours after dosing). To assess the pharmacokinetic parameters (AUC0→last, Cmax, tmax, and t½) of (R,S)-warfarin, (R)-warfarin, and (S)-warfarin, blood samples were obtained pre-dose, and then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hr post-dose. Parameters obtained when warfarin was given with eszopiclone were compared with those of warfarin given alone. The pharmacodynamics (prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]) of warfarin were assessed pre-dose and at 2, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hr post-dosing. The primary outcome variable was the AUCINR. Values obtained when warfarin was given with eszopiclone were compared with those of warfarin given alone.
Results: Twelve subjects (8 male) aged 21-62 years (mean 37.8) were enrolled and completed the study. The pharmacokinetic parameters, AUC0→last and Cmax, tmax for (R)-warfarin were similar between treatment periods (p=0.487 and p=0.121, respectively). The slight reduction observed in t½ with the combined treatment vs (R)-warfarin alone (43±14.1 h vs 50.8±11.0 h, respectively; p=0.051) did not affect systemic exposure to (R)-warfarin. Pharmacokinetic parameters for (S)-warfarin were not different between treatment periods. The pharmacodynamic assessments of AUCINR between treatment periods were not different. The INR curves for (R,S)-warfarin alone compared with (R,S)-warfarin given with eszopiclone were essentially super-imposable, suggesting a lack of pharmacodynamic interaction, further supporting the lack of pharmacokinetic interactions.
Conclusion: Administration of eszopiclone 3mg daily for 5 days did not affect the anticoagulant effect of a single 25-mg dose of warfarin. There was no pharmacokinetic or pharmacodynamic interaction of warfarin when co-administered with eszopiclone.

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Pharmacokinetic (PK) and Pharmacodynamic (PD) Effects of Eszopiclone: A Comparison of Healthy Non-Elderly and Elderly Adults

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Introduction: Eszopiclone is a novel, non-benzodiazepine, cyclopyrrolone agent under investigation to treat insomnia and has been shown to rapidly induce and maintain sleep. This study compares the pharmacokinetic profile and effect on psychomotor performance of a once daily (morning) dose of eszopiclone for seven days in healthy non-elderly adults compared with healthy elderly adults.
Methods: Two randomized, double-blind, placebo-controlled, two-center PK/PD studies in healthy male and female adults are reported: a parallel group study in non-elderly adults 18 to 45 years old (n=48); and a sequential panel design in elderly adults 65 to 79 years old (n=36). Eszopiclone doses evaluated were 1, 3, and 6mg (QDx7 days; 12 active, 4 placebo/group) in the non-elderly adult study and 1, 2, 3, and 5mg (QD x 7 days; 6 active, 3 placebo/group) in the elderly adult study. Plasma concentrations of eszopiclone were measured on Days 1 and 7. The Digit Symbol Substitution Test (DSST) was administered on Days 1 and 7 to determine extent and duration of the expected pharmacological sedative effect.
Results: Eszopiclone was rapidly absorbed in both groups, reaching peak plasma concentration levels (Cmax) at 1-1.25 hr post-dose. In both studies, steady state levels were reached at approximately 48 hours post the first dose. Cmax and AUC were approximately dose proportional following single and multiple dosing in both groups. For the 3mg eszopiclone dose in non-elderly adults, Day 1 and Day 7 PK curves were nearly superimposable. After 7 days of dosing in the elderly adults, the PK profile for the 2mg eszopiclone dose was similar to that of the 3mg eszopiclone dose in non-elderly adults. In both studies, the pharmacological effects did not change with multiple dosing over 7 days. In non-elderly adults, the expected PD effect (sedation) occurred rapidly and was maximal within 1 to 2 hours post-dose for eszopiclone 3mg, returning to baseline by 5 hours. In the elderly adults, mean DSST scores were maximal at about one hour post-dose for eszopiclone 2mg and returned to pre-treatment levels within 2 hours.
Conclusion: In both studies, plasma levels reached steady state by approximately 48 hours. The eszopiclone 2mg PK profile in the elderly adults is consistent and similar with the 3mg profile in the non-elderly patients. Based on the PK data and pharmacodynamic profile, 3mg is the targeted dose for the treatment of insomnia in non-elderly adults and 2mg eszopiclone is the targeted dose in elderly adults.

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Patient Functional Status and Tolerability of Long-term Modafinil in Shift Work Sleep Disorder

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Introduction: Shift work sleep disorder (SWSD) is characterized by

excessive sleepiness during nighttime work hours and/or insomnia during daytime sleep periods. In a 12-week, double-blind, placebo-controlled study, the wake-promoting agent modafinil significantly improved wakefulness in patients diagnosed with chronic SWSD and was well tolerated. The objective of the open-label extension period was to determine the continued safety, tolerability, and functional status.
Methods: This 12-month, open-label follow-up study enrolled 125 patients (age range, 21-62) with excessive sleepiness and International Classification of Sleep Disorders-defined chronic SWSD. Patients had completed the prior double-blind study. All patients were instructed to take modafinil at 200 mg/day, administered 30 to 60 minutes before the start of their regularly scheduled night shift. Safety and tolerability assessments included adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations. The effect of modafinil on functional status was assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ).
Results: 64 patients (51%) completed the study. Modafinil treatment was well tolerated in this long-term study. The most commonly reported AEs included infection (n=22; 19%) and headache (n=16; 14%). The most common adverse events related to modafinil treatment were headache (n=8; 7%), insomnia (n=8; 7%), and dry mouth (n=6; 5%). Most AEs (92%) were mild to moderate in severity. Three patients (3%) were withdrawn from the study because of AEs (prolongation of QT interval [in a patient with a history of prolonged QT interval], acidosis, and somnolence, respectively). No clinically significant trends were noted for clinical laboratory test results, vital signs, or physical examination findings in patients treated with modafinil. Modafinil was not associated with significant improvements in patient functional status as assessed by the FOSQ total score (mean change from baseline 1.5) and for individual domain scores (mean changes from 0.2 to 0.4).
Conclusion: Modafinil is well tolerated in patients with chronic SWSD. The adverse event profile was comparable to that reported in other long-term studies for patients with SWSD and other disorders of sleep and wakefulness. The lack of significance on the FOSQ results is in contrast to another study in which significant improvement in functional status was demonstrated particularly for the 300 mg modafinil dose.

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Post-Marketing Surveillance of Modafinil Abuse and Misuse

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Introduction: The predicted abuse potential of a medication, based on its pharmacology and sites of action, can vary widely from actual experience once the medication is marketed. Many medications over the years have been marketed as having low or no abuse or dependence potential, only to be found later to be widely abused or to cause dependence with regular use. Modafinil (Provigil), a wake-promoting agent, is not an amphetamine-related compound but does interact with the dopaminergic system, so its abuse potential was difficult to predict. For the past four years, the Haight Ashbury Free Clinics has conducted a study to ascertain what the actual experience of abuse and misuse has been of this medication among those for whom it has been prescribed as well as other groups that could become interested in its properties for non-therapeutic reasons. Modafinil has been widely used off-label to treat fatigue associated with many medical conditions, including MS, CFS, ADD, chronic pain, cancer treatment, and has also been used as part of medication regimens for depression, social phobia, and other disorders of primarily psychiatric etiology. Recently the FDA Peripheral and Central Nervous System Drugs Advisory Committee recommended expansion of the approved uses of modafinil, initially limited to excessive daytime sleepiness associated with narcolepsy, to also include obstructive sleep apnea and shift work sleep disorder.
Methods: The project uses a broad-net monitoring methodology to gather information on instances of abuse in identified high-risk populations (e.g., stimulant or polydrug abusers, youth, truck drivers, athletes, smart drug users) as well as among any other groups, including those prescribed modafinil for therapeutic purposes. Data sources include the Internet, medical literature, public and private information sources, addiction treatment professionals, law enforcement, and other key informants regarding their knowledge of any modafinil abuse patterns that may develop. Instances of possible abuse or misuse are independently evaluated by medical experts to determine if they represent actual abuse or dependence per DSM-IV-TR, misuse, or legitimate off-label use.
Results: No consistent pattern of abuse has emerged among any definable population of users although isolated cases of abuse have occurred. Therapeutically indicated use of modafinil among drug abusers has not resulted in a significant rate of abuse.
Conclusion: While physicians should consider the potential abuse liability of modafinil when prescribing it, especially to members of high-risk groups, the abuse liability of modafinil appears to be low.

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Patient Functional Status, Safety, and Tolerability of Modafinil in a 12-Month Open-Label Study in Patients With Chronic Shift Work Sleep Disorder

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Introduction: Shift work sleep disorder (SWSD) is characterized by excessive sleepiness during nighttime work hours and/or insomnia during daytime sleep opportunities. The wake-promoting agent modafinil significantly improved wakefulness in patients diagnosed with chronic SWSD and was well tolerated in a 12-week, double-blind, placebo-controlled study. The objective of the open-label extension period was to determine functional status of patients and long-term safety and tolerability of modafinil.
Methods: This 12-month, open-label follow-up study enrolled 166 patients (age range, 23–58) with excessive sleepiness and chronic SWSD (International Classification of Sleep Disorders), who had completed the prior double-blind study. Patients continued to work a minimum of 5 night shifts per month. All patients were instructed to take modafinil at 200 or 300 mg/day, administered 30 to 60 minutes before the start of their regularly scheduled night shift. The effect of modafinil on functional status was assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ). Safety and tolerability assessments included adverse events, clinical laboratory tests, vital signs, and physical examinations.
Results: Significant improvement in patient functional status was observed in the total score at endpoint (mean change in FOSQ from baseline = 2.4 with a 95% confidence interval of 1.91-2.83). Improvements were also seen at endpoint for the individual domains: activity level (0.5, 95% CI 0.44-0.65), general productivity (0.4, 95% CI 0.32-0.49), intimacy (0.4, 95% CI 0.26-0.51), social outcome (0.4, 95% CI 0.28-0.53), and vigilance (0.6, 95% CI 0.49-0.71). 118 patients (71%)

completed the open-label study. 162 patients (98%) were included in the safety analysis set. Modafinil treatment was well tolerated during this long-term study. The most common adverse events included headache (n=23; 14%), infection (n=21; 13%), and pain (n=18; 11%). Most adverse events were mild to moderate in severity. The most common adverse event related to modafinil treatment was headache (n=14; 9%). Nine patients (6%) were withdrawn from the study due to adverse events; most were due to adverse events related to the nervous system (eg, anxiety, nervousness, and insomnia). No clinically meaningful effects of modafinil were seen in clinical laboratory tests, vital sign parameters, and physical examinations.

Conclusion: Modafinil significantly improves patient functional status. The magnitude of change in the FOSQ total and individual domain scores was consistent with those seen in the double-blind phase of this study, which demonstrated statistically significant improvements for patients treated with the 300 mg dose of modafinil for vigilance, activity level, and general productivity, with trends toward significance for the 200 mg dose. Modafinil is well tolerated over time in patients with chronic SWSD. The adverse event profile is comparable to that reported in other long-term studies for patients with SWSD, narcolepsy, and residual sleepiness despite nCPAP use in obstructive sleep apnea.

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Tolerability of Modafinil in Disorders of Sleep and Wakefulness

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Introduction: Excessive sleepiness in disorders of sleep and wakefulness can be caused by sleep-wake dysregulation (eg, narcolepsy), sleep disruption (eg, obstructive sleep apnea [OSA]), or circadian misalignment (eg, shift work sleep disorder [SWSD]). Modafinil has been shown to improve wakefulness in patients with excessive sleepiness in narcolepsy, SWSD, and OSA (despite regular nCPAP use). The tolerability of modafinil was evaluated from 6 placebo-controlled studies in these disorders.

Methods: The tolerability data were combined from 6 placebo-controlled studies: 2 studies each in narcolepsy, SWSD, and residual excessive sleepiness in OSA. The duration of the trials was between 4 and 12 weeks with doses of 200 mg or 400 mg per day. Assessments included adverse events and effects of modafinil on either nighttime or daytime (for the SWSD studies) sleep (by polysomnography), blood pressure/heart rate, and electrocardiogram intervals. Clinical laboratory parameters included absolute neutrophil and white blood cell counts.

Results: 369 patients with narcolepsy, 292 with OSA, and 273 with SWSD received modafinil; 567 received placebo. Adverse events that occurred in ≥5% of patients and were greater for modafinil than placebo were headache (34% vs 23% for modafinil compared with placebo, respectively); nausea (11% vs 3%); rhinitis (7% vs 6%); nervousness (7% vs 3%); back pain (6% vs 5%); diarrhea (6% vs 5%); dizziness (5% vs 4%); dyspepsia (5% vs 4%); insomnia (5% vs 1%); and anxiety (5% vs <1%). Most adverse events were transient and mild to moderate in nature and occurred within the first month of treatment. The adverse event profile for modafinil was similar among the disorders studied, except for headache, which was more frequent in narcolepsy. Eight percent of modafinil and 3% of placebo patients discontinued treatment due to adverse events. In the modafinil treatment group, the most common adverse events leading to withdrawal were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (<1% each). Nighttime or daytime sleep was not adversely affected by modafinil as assessed by polysomnography. Modafinil had no clinically or statistically significant effects on blood pressure/heart rate, electrocardiogram intervals, or clinical laboratory evaluations (including absolute neutrophil/white blood cell counts) compared with placebo.

Conclusion: Modafinil is well tolerated in patients with excessive sleepiness associated with narcolepsy and SWSD and with residual excessive sleepiness in OSA. The tolerability profile of modafinil was consistent across the disorders studied. Modafinil has no clinically significant effects on cardiovascular and clinical laboratory parameters.

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Do Dreams Reflect Clinical Change in Psychotherapy

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Introduction: It has been demonstrated that dream content is highly regular reflecting demographic and psychiatric illness differences,trait and state differences as well as differences between individuals and night to night within an individual A question remains whether dreeeam cntent reflects psycotherapeutic change.
Methods: Dream reports were selected by M.G.from his long term psychotherapy or psychoanalytic caases.In Study#1 the dream reports were selected early and late in the treatment from 6 patients who had shown great improvement and 6 who had shown limited improvement.The dream pairs were presented randomly and without identification or associations to M.K. who had to sort them into 6 improved and 6 unimproved.M.G.then rank ordered the degree of improvement of the 12 patients.He selected the first and last dream in Study#2, an early and late dream on an important issue in Study#3 and a series of dream reports every 2 years in Study#4, those in Study#4 were from a different group of 12 patients.The task for M.K. was to rank order the patients' improvement based on the randomly presented dream pairs. He had assumed that eachstudy was from a different group of patients, actually Sudies#1,#2 and #3 were from one group and #4 from another.
Results: In Study#1, M.K.placed all patients correctly(Fisher exact probability p=.001).Two of 7 psychiatric in a dream course got 83% correctly placed.In Study#2, the Spearman correlation was r=.45,p=.069.In Study#3, the correlation was r=.41, p=.09 and in Study#4, r=.377.p=.11.
Conclusion: Dream reports without associations, context or the patient's history do reveal categorically progress or the lack of it in long term intensive psychotherapy or psychoanalysis. Dream reports may reasonably suggest the degree of progress in such therapies. The further regularity in dreaming these results demonstrate again raise doubt about dreaming being an organic delirium.

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Polysomnographic Variables Affecting Reported Dream And Nightmare Recall Frequency

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Introduction: Variables reported to affect reported dream and nightmare recall frequency include age, gender, collection method, arousal frequency, sleep stages, daytime sleepiness and the presesece of OSA. This study correlates selected demographic and polysomnographic variables postulated to affect dream recall frequency with the dream and nightmare recall frequency described by a grouping of sleep laboratory patients.
Methods: This study included 209 randomly selected patients undergoing complete night polysomnography at an AASM accredited sleep laboratory. These individuals completed an intake questionnaire assessing dream and nightmare recall frequency using a Likert scale from (1-5) with 1=never, 2=monthly, 3=weekly, 4=3X/week, and 5=nightly. Correlated variables included: age; gender; Epworth score; total sleep time (TST); sleep latency (SL); REM sleep time, percent and latency; Stage 3&4 minutes and latency; arousal index (ArI); apnea-hypopnea index (AHI); and periodic limb movement index (PLMI).
Results: Mean reported dream recall was 2.69 and mean reported nightmare frequency 2.26. Reported nightmare frequency (2.75) in the youngest age grouping (< 15 yoa) was significantly higher ($p < .01$) than in the oldest grouping (1.54) (> 75 yoa). Both dream and nightmare frequency showed consistent declines with increasing age. The grouping reporting no dream recall (N=23) had a significantly lower REM % ($p < 0.02$)when compared to the grouping reporting dream recall (N=176). Individuals reporting high dream recall (responses 4&5, N=41) had significantly higher levels of REM % ($p < 0.01$) compared to groupings reporting lower dream recall (N=168). Individuals reporting no nightmare recall (N=50) were found to have significantly lower mean REM% ($p < 0.02$) and REM sleep time ($p < 0.01$) compared to the grouping reporting nightmare recall (N=154). Individuals (N=55) with > 20% REM sleep had significantly higher levels of reported nightmares (2.55) than those with less than 20% REM sleep (2.18, N=161) ($p < 0.02$). Individuals with mean PLMI < 15 (N=154) had significantly higher reported dream ($p < 0.02$) and nightmare recall frequency ($p < 0.01$) compared to individuals with mean PLMI > 15 (N=55). Nightmare frequency was lower in patients with higher ArI ($p < 0.1$). Dream recall declined in patients with mean SL < 5 min. ($p < 0.1$).
Conclusion: This study indicates that in this sleep laboratory population reported dream and nightmare frequency declines significantly with increased PLMI. Patients with reductions in REM sleep had lower levels of reported dream recall frequency. REM sleep variables (% and minutes) in this population were consistantly and significantly correlated with respective increases and decreases in reported nightmare frequency.

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The Early Riser Gets The Dream Recall

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Introduction: A variety of dream researchers have suggested that arousal level is a crucial component when determining likeliness of remembering dreams. In 2003 Aeschbach et al. reported a longer biological night, defined by the onset and offset of nocturnal melatonin, cortisol, and temperature rhythms, for people who habitually sleep more than 9 hours ("long-sleepers") when compared to people who habitually sleep less than 6 hours ("short-sleepers"). Current research investigates the relation between habitual rise time, arousal times, morningness-eveningness type, and dream recall frequency.
Methods: Following initial phone screen, subjects were given a 2 weeks' supply of paper-based sleep journals to complete and a wrist worn actigraphy unit to wear. The sleep journal consisted of 8 questions to be answered upon waking each morning. The questions are as follows: bedtime, sleep latency, arousals during the night, rise time, total sleep time, how refreshed you feel after waking, was this a typical night of sleep, did you dream last night, and how many separate dreams do you remember? Following 2-weeks of sleep journals and actigraphy, subjects were divided into three categories based on journal reported total sleep time (TST): Long Sleepers (LS) TST > 525 minutes, Normal Sleepers (NS) 375 min < TST < 525 min, and Short Sleepers (SS) TST < 375 min. To date, 11 LS(28±10yrs, 6 females), 13 NS (27±8yrs, 6 females), and 18 SS (36±13yrs, 11 females) have participated in the study.
Results: Values for the main outcome variables are: Journal TST (LS 551 ±21min, NS 480±55min, SS 329±32min), bedtime (LS 24:11±1:08, NS 24:26±1:36, SS 24:30±1:12), rise time (LS 9:35±1:15, NS 8:45±1:44, SS 6:25±0:59), Horne and Ostberg Morniness-Eveningness Questionnaire (MEQ) (LS 45±6, NS 47±11, SS 57±6), and percentage of nights subjects recall a dream (LS 55.3±30%, NS 62±19%, and SS 68±29%). SS wake significantly earlier than both LS and NS and score significantly higher on the MEQ, indicating greater morningness. A lin-

ear regression with MEQ, rise time, and waking refreshed as explanatory variables and percent of nights a dream is recalled as the response variable yielded a significant full model (p=0.36 Rsq=.33). Greater dream recall was associated with increased feelings of refreshed, earlier rise times and, surprisingly, lower scores on the MEQ. There were no significant differences between the groups in subjective or objective arousals, or sleep efficiency.
Conclusion: Our preliminary results expand on the idea that arousal level is related to dream recollection. We found the combination of three variables, MEQ score, rise time, and waking refreshed, predicted dream recall frequency. SS are more likely to fit the profile of someone likely to remember dreams because they are "morning" people who wake earlier. Aeschbach et al.'s report suggests dream recall may also be higher in SS due to an earlier offset of the biological night in SS, who therefore naturally have higher arousal levels in the morning. These results suggest chronotype may be the biological underpinning behind findings that arousal levels can predict dream recall ability. Future studies examining dream recall may need to consider chronotype as a confounding variable.

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Memory Processing Reflected In Dreams From Rapid Eye Movment Sleep

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Introduction: It has been reported in both animals and humans that auditory cueing during rapid eye movement (REM) sleep enhances memory processing. Smith and Weeden reported superior memory for a cognitive procedural logic task when auditory cueing (clicks) accompanied acquisition. These clicks were again presented during subsequent REM sleep such as to be coincident with the maximum deflection of the actual rapid eye movements. The aim of the present experiment was to examine the mental content (dreams) of participants exposed to this memory enhancing process.
Methods: After an acclimatization night, twelve female undergraduate university students learned the mirror trace task. Group 1- Five subjects were exposed to the sound of a ticking alarm clock while learning the task. During the subsequent sleep night, participants received approximately five hundred 70 db clicks via a mini-earphone, that coincided with the maximum deflection of the actual rapid eye movements. Group 2 - Four participants were also exposed to the 70 db clicks after task acquisition, but these clicks were delivered during "quiet" REM, when no rapid eye movements were occurring. Group 3 - Three participants learned the task as did the others, but no clicks were delivered at any time during the night. Subjects were all awakened after 50-80% of the REM sleep periods were believed to have been completed and asked to report any dreams they might have been having. Participants were all retested 1 week later on the mirror trace task.
Results: While the number of dreams per group did not differ, the dream reports of the participants in Group 1 were found to be significantly longer (more words) than the reports of the other two groups [$F(2,9) = 5.96$, $p = .023$]. An analysis of the dream content using the "driving" theme revealed a significantly greater proportion of references to cars, driving, steering, etc. for Group 1 [$F(2,9) = 3.90$, $p = .06$]. Using the Hall-Van DeCastle content analysis system, Group 1 was found to have a higher proportion of elements referring to Recreation (IR) than the other two groups [$F(2,9) = 5.85$, $p=.024$]. Groups did not differ on amount of Total sleep or any of the Stages of sleep (1, 2, 3 and 4 or REM). Group 1 was not superior to the other groups on task retest.
Conclusion: The presentation of cues during REM sleep to coincide with maximum rapid eye movement deflection (Group 1) induced longer dream reports. As well, the reports appeared to symbolically relate to the nature of the learning task, having such themes as "trying to stay on the road" (trying to stay between figure lines in the mirror trace task). There were also more references to competitive sports by Group 1. While the behavioural results did not replicate the earlier study, it is likely that interrupting the REM sleep periods to obtain verbal dream reports interfered with the previously observed memory enhancement effect.

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The Perception of Self- versus Experimenter-Produced Tactile Stimuli when Waking from REM and NREM Sleep: Implications for the Psychophysiology of Dream Formation

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Introduction: Blakemore et al (2000; The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychological Medicine, 30, 1131-1139) have shown that mild tactile stimulation of normal subjects by an experimenter is rated as more intense, tickly and pleasant than the same stimulation initiated by the subject, which they hypothesise occurs because self-produced sensations are predicted, and thus attenuated. However, individuals with schizophrenia or other psychosis experiencing auditory hallucinations and/or passivity phenomena did not show this attenuation, just as they may not appreciate that their hallucinations are self-produced. Believing in the reality of hallucinations, at least while they are occurring, is also a characteristic of dreaming. We investigate whether the lack of stimulus attenuation found in people with hallucinations/passivity phenomena in Blakemore et al is also associated with REM sleep and REM sleep dreaming. We utilise the methodology that cognitive characteristics of REM and non-REM sleep can be tested while subjects are waking from those sleep stages, in that the neurochemistry of the sleep stage persists briefly after waking. For example, REM sleep awakenings have an advantage over non-REM sleep awakenings for solving anagrams and accessing remote associates (Walker et al, 2002; Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. Cognitive Brain Research, 14, 317-324). We propose two hypotheses. Hypothesis 1: self-stimulation ratings would be greater than ratings of experimenter-stimulation after REM sleep than after non-REM sleep, as the former stage of sleep is the most supportive of dream production; Hypothesis 2: the same as hypothesis 1 except that the REM period has to be accompanied by a dream, and the NREM period has to have no dream reported.
Methods: 14 participants (F=9, M=5, ages 18-21) were awoken 10 minutes into REM and non-REM sleep periods (counterbalanced: REM2 and NREM4 or NREM3 and REM3). A later REM awakening was performed if a dream was not reported for the REM awakening. Immediately upon waking, the participant and experimenter alternated in producing stimulation of the left palm of the participant using the Blakemore et al stimulation device, which allows the same stimuli to be caused by the experimenter (male) or by the participant. The participant then rated the self- and also the experimenter-stimulation on three dimensions: Intense, Tickly, and Pleasant, on a 10 point scale of 0 = not at all to 10 = extremely. These three scores were summed for each condition for the analysis. The self- and experimenter- stimulation and rat-

ings block lasted approximately 40 seconds.
Results: Hypothesis 1 was not supported: mean (experimenter minus subject) stimulation score for REM sleep condition = 0.39 (SD=4.11), for NREM sleep condition mean score = 1.07 (2.62); awake baseline recorded in the evening and morning mean score = 0.07 (.60). For Hypothesis 2, 9 subjects (8 females, 1 male) had a REM period with a dream and a non-REM period without a dream. Due to highly outlier baseline score for the male subject, only the females' results are analysed. For REM with dream condition mean (experimenter minus subject) stimulation score = -1.13 (SD=2.10), and for NREM with no dream condition mean stimulation score = 0.88 (SD=1.55), a significant difference on a Wilcoxon test, Z=2.21, p=.01.
Conclusion: Ratings for self-stimulation exceed ratings for experimenter-stimulation immediately after REM dreaming compared to NREM periods without dreaming, indicating psychophysiological deficits in self-monitoring may be necessary for, or accompany REM dream formation, and these deficits persist briefly into waking. These deficits may also account for the passivity and lack of intentionality in dream phenomenology.

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Dreaming In Young Children And Dream Bizarreness

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Introduction: In the 1990s some authors have focused on formal aspects of children dreams, particularly on dream bizarreness (impossible and/or improbable features of dream content). Although several studies have observed that the dreams of children in preschool age are realistic and without bizarre contents, it was recently suggested that these dreams have a substantial frequency of bizarre elements similar to that of adult dreams. This paper presents the results about children dreaming bizarreness of an extensive study on children dreams based on questionnaires compiled by parents.
Methods: The questionnaire used considers three groups of questions: a. questions about parent compliance with dreams; b. questions about children dreaming, particularly the latest dreams they have had; c. questions about the children sleeping habits. 1148 questionnaires were distributed to parents in several Italian schools. 652 returned to the experimenter (return rate = 57%), 565 were usable (usability rate = 49%) (255 female / 310 male, aged 3 to 8). In 325 questionnaires (57%), the parents wrote down the last dream reports of their children. Parents classified the dreams as follows: 1. - ordinary and realistic-, 2. -realistic but with some strange elements- and 3. -strange and improbable-.
Results: The most frequent dreams in younger children (3 to 5 years old) were - ordinary and realistic- (46%, n 62), 38% (n 52) were classified as - realistic but with some strange elements- and only 16% (n 22) were - strange and improbable-. In the older age group (6 to 8) dreams were classified as follows: 38% (n 64) -ordinary and realistic-, 34% (n 57) as -realistic but with some strange elements-, and 28% (n 46) as -strange and improbable-. The differences between age groups were close to statistical significance ($\div = 5.619$, df = 2, p = .060)
Conclusion: In keeping with previous studies, these data suggest that the dreams of young children are substantially simple and realistic. Bizarre dreams (-strange and improbable-) like those of the adults are rare. The dreams of older children seems to show more bizarre features. Previous studies have showed that the increment of dream bizarreness in older children depends much on the measurement used for bizarreness. The results of this study and those of previous literature show that the earliest forms of dreaming are not bizarre. This means that dream bizarreness cannot be considered a constant formal property of all dreams. From this viewpoint is difficult to consider dream bizarreness as an invariant expression of the physiologic conditions of the brain during sleep (i.e., neurobiological theory). These results are instead more in line with the cognitive and psychoanalytic approach, according to which dream bizarreness is affected by cognitive and personality factors of growth.

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Threat Simulation In Nightmares

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Introduction: Revonsuo (2000) put forth an intriguing and detailed evolutionary theory of dreams which stipulates that the biological function of dreaming is to simulate threatening events and to rehearse threat avoidance behaviors. In this theory, dreaming is viewed as both an organized and selective simulation of the world. Our group previously showed that many recurrent dreams do not depict situations critical for one's physical survival or reproductive success. Even when recurrent dreams depicted such situations, the threats were rarely realistic and the dreams rarely contained successful avoidance responses. The goal of the present study was to evaluate the extent to which the main postulates of Revonsuo's theory apply to nightmares.
Methods: The data presented are based on the content analyses of 174 nightmares. The nightmare reports were obtained from 118 adults (90 women aged 32.2 ± 12.8; 15 men aged 33.6 ± 10.8; 13 subjects did not indicate their age) who had kept a written dream log for 2-4 consecutive weeks as part of an unrelated series of studies on personality and dream content. To avoid any overrepresentation of subjects reporting many nightmares, a maximum of two nightmares were randomly selected from each participant's dream log. To be included in the present study, a nightmare had to be described in sufficient detail to allow a content analysis of the dream's setting, its affective tone, and the characters present. All nightmares were scored using a slightly modified version of the rating scales elaborated by Revonsuo to identify and describe threatening events in dreams.
Results: 110 of the 174 nightmares (63%) contained threatening elements. In about half (52%) of the nightmares, the nature of the threatening event was such that the subject was likely to have personally experienced it in waking life or to have heard about somebody in his environment who had encountered the threat. The dreamer was the target of the threat in 87% of the cases and the dangers were life-threatening or physically perilous 72% of the time. Specific thematic subcategories for the threats included aggressions (42%), escapes/pursuits (22%), physical/environmental anomalies (14%), accidents/misfortunes (12%), failures (4%), emotional difficulties (2%), disasters (1%) and unclassified threats (3%). In a majority (77%) of nightmares with threatening events, subjects participated actively in the course of the event and presented a possible and reasonable fight or flight response. Nevertheless, threats were twice more likely to adversely affect the dreamer than to be successfully avoided or dealt with.
Conclusion: Our data on nightmare content provide partial support for the idea that the evolutionary function of dreams is be to simulate threatening events and to rehearse threat avoidance skills.

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Classification Of Physiological Activity During Sleep-Onset Process And Its Relationship With Mentation Properties

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Introduction: The objective of this study is to classify patterns of physiological activities underlying generation of sleep-onset (SO) mentation and to investigate the relationship between these patterns and mentation properties. It is hypothesized that sleep-onset mentation will be characterized by multiple physiological activity patterns specific to sleep-onset processes.
Methods: SO mentation was repeatedly sampled by awakenings after 5-sec of SO stage 4 or 5 had elapsed (Hori et al., 1991, 1994; flattened EEG; low voltage theta wave bursts). Subjects were asked to asses properties of their mentation by ratings on bipolar adjective scales (DP-R; modified from Dream Property scale; Takeuchi et al., 2001). This procedure was repeated either until the number of awakenings reached 10 or 2 hours had passed since first lights-out. Nineteen standard EEG channels, vertical and horizontal EOG and bipolar submental EMG were digitized and recorded at 256 Hz. (1) FFT analyses were performed with 1-sec FFT length using a cosine window and 50% overlap a) on the EEG for 6 bandwidths; 4-8, 8-12, 12-16, 16-24, 24-28Hz, b) on the EOG (vertical, horizontal) for a single 0.3-2.5 Hz bin, and c) on the EMG for total power. FFTs were averaged for 5-sec epochs preceding each awakening. Due to skewed distributions, FFT power values were log-transformed. (2) Factor analysis (Promax rotation) was performed on 40 DP-R rating scales for a total of 233 SO mentation reports from 31 subjects. (3) Cluster analysis on SO samples was performed with 8 measures (EOG potentials, EMG total power, theta (4-8Hz) in Cz, 2 alpha bands (8-12, 12-16Hz) in O2, spindle activity (12-16Hz) in Cz, beta (24-28Hz) in Cz), that were averaged for the 5-sec preceding each awakening. Based on the pattern of these measures, cluster analyses (K-means) were performed which classified 5-sec samples preceding awakenings into 5 groups (G1-G5): G1 consisted of increased EOG, EEG and EMG, G2 consisted of decreased EOG and EEG, but increased EMG, G3 consisted of decreased alpha and beta EEG, average spindle EEG in Cz, and increased theta EEG but no EOG, G4 consisted of increased EOG, average EEG and EMG, and G5 consisted of average EOG, increased alpha EEG in O2, average theta, alpha, beta EEG in Cz, and no EMG. (4) One-way ANOVAs were performed among the 5 groups using the DP-R scores as dependent variables.
Results: Four factors were extracted using eigenvalue > 2.0. Measures with high loadings clearly defined 4 factors corresponding to the 4 major properties of SO mentation: 1) Emotion, consisted of 13 items (e.g., unpleasant-pleasant, depressing-cheerful, disgusting-enjoyable), 2) Chaos, consisted of 11 items (e.g., organized-unorganized, orderly-chaotic, forgettable-memorable, rational-irrational), 3) Unrealistic, consisted of 7 items (e.g., uncommon-common, normal-abnormal, ordinary-extraordinary, usual-unusual), 4) Dynamism, consisted of 9 items (e.g., calm-busy, static-dynamic, passive-active, pale-colorful etc.). One-way ANOVA showed a significant group effect for the Dynamism factor ($F(4,166)=3.060$, $p<.05$). Post-hoc analyses indicated significant differences in DP-R score between G2 (+.432) and G4 (-.136) and marginal differences between G4 (-.136) and G5 (+.376). Compared to G4, which comprised the majority of the samples (63.4%), G2 (19.5%) and G5 (8.7%) were unique especially in the opposing direction of EMG and EEG activities (G2; relatively high EMG with less EEG, G5; least EMG with high alpha EEG). In other words, two distinct physiological profiles (G2, G5) were both associated with an increase in Dynamism descriptors (busy, dynamic, active, vivid, colorful). Apparently more than one mechanism (e.g., arousal intrusion, covert-REM) may underlie one and the same SO mentation property.
Conclusion: The results support the possibility that SO mentation can be characterized by more than one physiological activity pattern specific to sleep-onset processes.

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Dreaming In Childhood

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Introduction: While studies on children dreaming have proved to be useful for our understanding of dream processes and psychological child growth, to date only a few studies on small groups of subjects have been conducted. This paper summarizes certain significant results of an extensive study on children dreaming conducted through questionnaires filled by parents.
Methods: The questionnaire used considers three groups of questions: a. questions about parent compliance with dreams; b. questions about children dreaming, particularly the latest dreams they have had; c. questions about the children sleeping habits. 1148 questionnaires were distributed to parents in several Italian schools. 652 returned to the experimenter (return rate = 57%), 565 were usable (usability rate = 49%) (255 female / 310 male, aged 3 to 8). In 325 questionnaires (57%), the parents wrote down the last dream reports of their children.
Results: The first dream. The first dream story was reported by a little girl of 2 years and 11 months: -The girl and her dog were running towards the road and then the dog invited her to climb up and go faster, but there was an officer-. Dream recall. Dreams recalled by children in previous month were: none (32.6%), 1-3 dreams (49.4%), 4-5 (9.9%), 6-9 (4.7%), 10-20 (3.4%). Feelings during dream narration. While reporting dreams, the children frequently appeared quiet or appeased (74%), more rarely anxious (21%), and gloomy (5%). Dream length. Parents classified dream stories as follows: -brief story- (60%), -brief sentence- (16%), -long sentence- (12%), -long story- (7%), -long and elaborates story- (5%). Dream characters. The most frequent characters were -family members- (57%), -animal characters- (46%), -known children- (44%) and -TV and famous characters- (20%). Self-representation. Children start to picture themselves in their dream scenario already between 3-5 years of age. In particular, they appear as -main characters- (56%) and as -side characters- (26%). Only in 9% of dreams the dreamer was not present. The same situation was found in children aged 6 to 8. Dream setting. The most frequent dream setting was -home- (23%). -school- was present in 13% and -recreational setting - in 10%. However, the setting were frequently -vague- (27%). Social interaction. Dreams frequently (67%) show social interaction from children aged 3-5.
Conclusion: These results are mainly in line with those of previous studies based on interviewing directly the children about their dreams (home and school settings). Certain features (e.g. dream length, percentage of animal characters, home setting and vague setting) are also consistent compared to the children REM dreams. The results on self-representation are in keeping with studies on child dreams collected at school and at home, but they differ from the results on self-representation in REM dreams. These results show that this method provides reliable indications on children dreams that are mostly in line with the results of studies conducted with conventional methodologies (e.g. dreams collected upon morning awakening at home).

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How Confident are People in Judging Whether the Events or Emotions of a Nightmare Woke Them Up?

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Introduction: There is debate about whether to include in the definition of nightmares the criterion that the person had to be awoken by the events or emotions of the nightmare. Zadra and Donderi (2000; Nightmares and bad dreams: Their prevalence and relationship to well-being. J Abnormal Psychology, 109: 273-281) found that nightmare frequency using this criterion is a better index of low well-being than is nightmare frequency without using the criterion, but other studies have not found this. We aimed to ascertain how confident individuals are in deciding that a dream woke them, to assess whether waking is more likely to be caused by unpleasant than pleasant dreams, and to compare correlations of well-being with nightmare frequency using and not using the criterion.
Methods: 42 participants (33 females, 9 males, mean age = 21.8 years, SD=6.55) reporting at least one nightmare per month completed the Spielberger State Trait Anxiety Inventory and the General Health Questionnaire (a measure of current stress and general well-being). They made a retrospective estimate of their nightmare frequency, using the definition: very disturbing dreams, involving any unpleasant emotion, which are usually vividly recalled, and also estimated their frequency of nightmares where the nightmare wakes them up. They then kept a dream log for 14 nights, each morning answering the following items: 1. Did you have a dream last night? 2. How pleasant/unpleasant was the dream? (7 point scale: 1 = very pleasant to 7 = very unpleasant.) 3. Did the emotion of the dream wake you up? 4. Rate how certain you are of your answer to question 3. (5 point scale: 1 = very uncertain to 5 = very certain.)
Results: Trait anxiety correlated with retrospective nightmare frequency (r=.35, p=.025) but not with retrospective nightmare frequency using the awakening criterion (r=.21). It correlated with log nightmare frequency (defined as dreams rated 6 or 7 on the unpleasantness scale; r=.33, p=.033) and log nightmare frequency using the awakening criterion (r=.36, p=.019). State anxiety and stress did not correlate significantly with these nightmare variables. On the dream log 18 participants had at least 3 instances of a dream that woke them up and at least 3 instances of a dream that did not wake them up: these participants are used for the following analyses. Mean confidence that dream content did not cause awakening = 3.90 (SD=.75), and mean confidence that content caused awakening = 4.40 (SD=.62), paired t-test t =2.82, p=.012. Mean dream pleasantness when content did not cause awakening = 3.70 (SD=.88), and mean pleasantness when content caused awakening = 4.89 (SD=1.33), paired t-test t=4.21, p=.001. Mean confidence when stating that the dream caused awakening was insignificantly correlated between-subjects with mean dream unpleasantness (r=.23).
Conclusion: Individuals have very high confidence when they judge that the events or emotions of a dream woke them up. If this can be taken as evidence that they are accurate in ascribing their awakening to the events of the dream, there may be validity in including the awakening criterion in the definition of nightmares, especially as these awakenings are more likely to result from unpleasant than pleasant dreams. However, frequency of nightmares using the awakening criterion did not in this study have a greater correlation with waking well-being than did nightmare frequency not using the criterion.

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Dreams of Recently Hospitalized Trauma Patients and Their Relationship to PTSD

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Introduction: Disturbing dreams or nightmares are associated with posttraumatic stress disorder (PTSD) and can occur prior to when the diagnosis can be established. It has also been posited that dreams may have an adaptive role in the emotional processing of trauma experiences. This study undertook to identify first, how the dream content from the combined sample differed from the content of a normative dream sample and, second, whether the dream content of patients who subsequently developed PTSD differed from the dream content of those patients who did not develop PTSD.
Methods: Dreams of recently hospitalized trauma patients were recorded following admission to Level I trauma units (University of Miami Medical Center and Dartmouth-Hitchcock Medical Center in Lebanon, NH) for assault or accident-related injuries. Participants were screened and evaluated within two weeks of their admission with a battery of tests including the Clinician Administered PTSD Scale (CAPS). Patients were assigned to either a PTSD group (full and subthreshold) or a No-PTSD group based on their follow-up CAPS at two months post-injury. Dreams were hand-coded by a rater blind to group assignment using the Hall and Van de Castle (1966) rating system. A maximum of 3 dreams from each patient reported within one month of the injury were utilized for purposes of this study. Dreams were combined and compared to normative data from a non-clinical population. The combined dreams of the two study groups were then compared to each other. Variables examined included presence of aggression, friendliness, sexuality, good fortune/misfortune, emotions, successes/failures and self-negativity, a global measure of negative content related to the dreamer. Analyses of group differences were done using an h-statistic to compare frequencies and alpha was set at .05.
Results: A total of 82 dreams from 47 patients were analyzed. The PTSD group (n = 20) had a mean number of 1.75 dreams compared to a mean of 1.78 in the No-PTSD group (n = 27). Dreams of all trauma patients combined had significantly less aggression, friendliness, sexuality, and good fortune (all $p < .001$), and more physical aggression ($p = .003$), bodily misfortune ($p = .01$) and self-negativity ($p = .02$) than the normative sample. When the patients were subsequently assigned to groups and compared to each other, the PTSD group had significantly more misfortune ($p = .006$), bodily misfortunes ($p = .028$) and negative emotions ($p = .003$) present in their dreams than the No-PTSD group. Other comparisons showed that the PTSD group had a strong trend towards increased self-negativity ($p=.056$).
Conclusion: To the extent that dream content reflects preoccupation with recent stressful events, these findings support the formulation that the dreamer in the aftermath of trauma is more cognitively focused on the trauma as opposed to normative populations whose dreams are focused on other content. Furthermore, the finding that patients who are not developing PTSD have much less negative content and negative emotional tone in their dreams, suggests that their dreaming is more emotionally adaptive and may represent successful processing of traumatic events.

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Content Analysis of Nightmares

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Introduction: Although numerous studies have investigated different aspects of nightmares, (e.g., frequency, association to various measures of psychopathology, treatment approaches) no systematic analysis of their content has appeared in the literature. The first goal of the present study was to evaluate the content of nightmares using standard Hall and Van de Castle dream content scales. The second goal was to establish a classification of nightmares' thematic content.
Methods: Written nightmare reports containing 25 words or more were obtained from 2-4 week dream logs completed for a series of studies on dream content and personality. To avoid an overrepresentation of nightmares from individuals reporting many nightmares, only one nightmare was randomly selected from each participant's dream log. The current sample was limited to 125 nightmares reported by 125 women (mean age 31.6 ± 11.2). Dream content was evaluated using the objective content analysis system developed by Hall and Van de Castle. Specifically, each nightmare report was scored using the following scales: Success and Failure, Good Fortune and Misfortunes, Friendly and Aggressive Interactions, Settings, and Dream Affect. Categories for the classification of the thematic content of nightmares were based on pilot data as well as a modified version of the Typical Dreams Questionnaire.
Results: The nightmare reports contained an average of 163.4 ± 133.4 words. The frequency of positive dream content categories was: success (8.8%), good fortune (1.6%), and friendliness (25.6%). The frequency of the corresponding negative dream content scales was: failure (12.8%), misfortunes (64.8%), and aggressive interactions (67.2%). A greater number of nightmares were described as occurring in indoor settings (64.8%) than in outdoor ones (34.4%) and 1 nightmare report did not contain a setting. Apprehension was the most frequently reported emotion (61.6%), followed by sadness/helplessness (15.1%), anger (8.8%), frustration (5.6%), and confusion (3.2%). In terms of thematic content, the five most frequently observed categories were: physical aggression (26%), ominous mood (12%), failure/helplessness (10.4%), interpersonal conflicts (8.8%), and being ignored or rejected (6.4%). Other themes occurring 5% or less included being chased but not caught, presence of demons, frightening insects or spiders, health problems or concerns, being stuck or trapped, and accidents.
Conclusion: To our knowledge, this is the first time a standard dream content analysis has been applied to nightmares. The data indicate that nightmares: a) sometimes contain positive dream elements; b) tend to unfold in indoor settings, and c) are frequently characterized by misfortunes and aggressive interactions. Consistent with previous reports, our results show that nightmares can contain primary emotions other than fear. Contrary to many case reports, our thematic categorization shows that nightmares can contain a wide range of themes beyond those of pursuit and physical aggression. Since the data presented are based on reports from female participants, whether or not similar content patterns exist in men's nightmares remains to be determined.

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The Frequency of Dreams and Nightmares After Brain Injury

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Introduction: Neuropsychological assessments of patients suffering brain lesions have offered insight into the neurological organisation of dreaming. Solms (1997; The neuropsychology of dreaming) found that 38% of patients with diffuse head injuries and lesions with other etiologies reported the absence of dreaming. Bilateral white-matter lesions in the ventromesial frontal region or lesions of the inferior parietal region of either hemisphere were associated with a cessation of dreaming. 7.9% of patients reported experiencing recurring nightmares, which Solms associated with temporo-limbic lesions.
Methods: Twenty-three patients who had suffered a head injury (Male= 16, Female = 7, mean age 41.87 (SD=13.28), range 20-66) were recruited from a forensic neuropsychology clinic, the majority (69.9%) had sustained head injuries in road traffic accidents. Mean age at injury was 38.61 years (SD=13.97, range 17-64), mean time since injury was 44.9 months (SD= 32.92, range 14-176). All patients had evidence of post-traumatic amnesia and loss of consciousness, indicative of diffuse axonal injury. Some had CT or MRI scan evidence of contusional injuries to one or both frontal lobes. Patients completed a neuropsychological examination, including tests of frontal and spatial cognition, depression and anxiety, and a questionnaire assessing frequency of dreams, nightmares and night terrors.
Results: 39.1% of patients reported that they did not dream, which is comparable to Solms' finding of 38% in his sample. This contrasts with the rate of not reporting dreams in normal populations of 6.1% (Borbely, 1984; cited in Strauch & Meier, 1996; In Search of Dreams) and of 6.5% in a sample of sleep clinic patients (Pagel, 2003; Non-dreamers. Sleep Medicine, 4, 235-241) who had a similar mean age (43.4 years, range 10-75) to ours. Absence of reporting dreaming was not related to scores on frontal or spatial cognitive tests, nor with depression or anxiety. 39.1% of patients reported the occurrence of repetitive nightmares compared to only 7.9% in the Solms study, and 37.5% reported a least one nightmare per month, which is in excess of the 5% estimate from the general adult population (American Sleep Disorders Association, 1990; The international classification of sleep disorders). 21.7% of patients reported at least one night terror per month, which again is in excess of the 3.5% estimate from the general adult population (Hublin et al, 1999; Limits of self-report in assessing sleep terrors in a population survey. Sleep, 22, 89-93).
Conclusion: Frequency of nightmares (recurring and non-recurring) and night terrors is increased following head injury, as is the incidence of reporting that one does not dream. The high proportion of nightmares and repetitive nightmares may be due to the emotionally traumatic nature of the accident as well as to the brain injury sustained. Previous literature suggests that changes in dream frequency may provide useful indicators of the course and quality of recovery from head trauma, as this reflects changes in cerebral functioning, and hence asking patients about dream frequency may be clinically useful in predicting psychological aspects of recovery.

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Qualitative Differences In Events Incorporated Into Dreams Either Immediately Or After A One-Week Delay

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Introduction: Temporal relationships between daily events and their incorporation into dreams are characterized by two types of effects: the day-residue effect (incorporation of event elements from the preceding day) and the dream-lag effect (incorporation of elements from about one week prior to the dream). This study examines whether specific qualities of events predict whether they will be incorporated either immediately (day-residue) or with a delay (dream-lag). Qualities of events were selected on the basis of competing hypotheses explaining the delayed incorporation effect, i.e., experimental confound, social adaptation, spatial memory processing, problem resolution, Zeigarnik effect. Possible experimental confounds included the recurrent nature of some life events (e.g., weekly activities) and the fact that the experiment lasted for 1 week.
Methods: 470 Introductory Psychology students recorded dreams for seven days. Subjects were asked to recall events that had occurred on a randomly determined day (1 to 7) prior to the most recent dream that they could remember well. To obtain a sample with both good dream incorporation and good event recall, we included only subjects who rated degree of correspondence between the dream and the selected event as > 3 and their confidence in recall of the event as > 4 (10-point scales). Among the 139 selected subjects (M=19.59 ± 2.10 years), 71.9% were female and 23.0% male. To maximize N for males, three groups were formed: Day-residue (Days 1-2; N=61), Control (Days 3-4; N=27) and Dream-lag (Days 5-7; N=51). Two judges blind to group scored each event on eleven scales using 5-point probability scales (1=none, 2=weak, 3=average, 4=high and 5=certain): weekly recurrence, other-than-weekly recurrence, interpersonal relationships, unresolved problem, resolved problem, negative and positive emotions, experiment, school, spatial location and self-actions. Interjudge reliabilities for a subsample of 75 events produced satisfactory intraclass correlations (r=0.5113 to 0.7809) for all scales except resolved and unresolved problems, which were excluded. Temporal Groups (Day-residue, Control, Dream-lag) were compared using Kruskal-Wallis and Mann-Whitney tests on the remaining 9 scales.
Results: Differences were found only for scales derived from the spatial memory processing and social adaptation hypotheses. Contrasts revealed significant differences between only the Day-residue and Dream-lag groups for interpersonal relationships (U=707.50; p=0.001), spatial location (U=745.00; p=0.005) and positive emotions (U=782.00; p=0.012), with the Dream-lag group demonstrating a higher likelihood to involve these kinds of events.
Conclusion: No support was found for either version of the confound hypothesis. However, results for references to interpersonal relationships and positive emotions support the notion that adaptation to social situations is reflected in delayed incorporations. Further, findings for references to spatial locations support the notion first advanced by Jouvet (1979) that spatial features of the environment are dealt with by a specific type of delayed memory process for spatial imagery. These findings begin to clarify how dreaming may function to mitigate stress or facilitate memory consolidation.

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Active Participation in Dreams, Active Coping and the Development of Post-Traumatic Stress Disorder

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Introduction: There is controversy about the psychological significance of dream content. Helplessness is a key emotional component of post-traumatic stress disorder (PTSD). Active participation is a measure of dream content that focuses on control, rating the degree to which a dreamer influences the outcome or is a passive recipient of events in a dream. Active coping is a measure of problem-focused approaches to decrease the negative effects of stress, and may be a conscious, self-reported analogue of active participation. Because active coping style and active participation in dreams indicate sense of control, we hypothesized that trauma survivors with higher scores in both measures would be less likely to exhibit PTSD.
Methods: We studied 47 subjects (31 males, 16 females, mean age 34.0) who sustained injuries from recent life-threatening events [62% (N=29) motor vehicle accidents, 23% (N=11) impersonal assaults and 15% (N=7) work-related accidents]. Patients were recruited while hospitalized, following medical stabilization. Participants were required to have recall of the trauma and to have experienced the event as threatening. Head injuries and intoxication at the scene, Axis I psychiatric disorders, and use of psychotropic medication during the month preceding the trauma were bases for exclusion. Participants were assessed for PTSD severity, coping, and were asked to report any recent dreams. Patients were reassessed for PTSD six weeks later. Evaluators rated active participation in dreams on a scale from 0, in which the dreamer is not present in the dream, to 4, in which the dreamer plays an active role and greatly controls the nature of events in the dream. The intraclass correlation for rater reliability was .82. Active coping is a subscale of the COPE assessment, and asks patients to what degree they have been "concentrating efforts on doing something about the situation" and "taking action to try to make the situation better." Pearson correlations were calculated between active participation in dreams, active coping and PTSD severity at initial and follow-up assessments.
Results: There was a negative correlation between active participation in dreams and initial PTSD (r=-.34, p=.02). Active participation in dreams and final PTSD did not significantly correlate. Also, active coping and initial and final PTSD were not significantly correlated.
Conclusion: The relationship between active participation in dreams and less severe PTSD symptoms is consistent with emotional processing theories of dreaming.

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Circadian Influences on Sleep Mentation

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Introduction: Discovery of the powerful association between dreaming and the REM phase of the REM-NREM sleep cycle 50 years ago initiated the modern era of dream science. However, the strong association of dreaming with that cycle, coupled with the high salience of its EEG-EOG markers and the well-described pontine-cortical circuits that drive the cycle, have detracted from the search for other brain cycles that

might drive the dreaming process. The present experiment shows that the slower diurnal sleep-wake cycle can have an effect on the quantity of mentation reported equal in power to the REM-NREM cycle. The activation effects of the two cycles sum, so that the active phase of both produces longer dream reports than either cycle by itself.

Methods: Twenty subjects each gave 2 REM and 2 NREM mentation reports: one REM/NREM pair at the nadir of their circadian body temperature rhythm (estimated as 2.7 hours before average waking time based on work by Czeisler, 1990) and the second pair a minimum of one hour after their mean home waking time. Reports were scored for Word Information Count (WIC), a report-count that eliminates repetition, nonwords, and words that do not provide new information about the sleep mentation. To minimize the positive word count skew for statistical analyses, WIC was log transformed to produce logWIC.

Results: Late morning reports were substantially longer than reports from the circadian nadir ($F1,19 = 19.40$, $p<.001$). The effect size, .51, was very large. Averaged over nadir and late awakenings, reports were, as expected, significantly longer for REM than NREM ($F1,19 = 12.73$, $p=.002$), with an effect size of .40. There was no interaction between circadian time and sleep stage, indicating that the effects of the two cycles were additive. That is, circadian time had a similar effect on both REM and NREM reports.

Conclusion: The effect of circadian activation reported here is larger than those reported by earlier studies in our lab. We attribute this larger effect to a more accurate estimate of the circadian nadir. Indeed, the circadian effect is actually larger than the main REM/NREM effect. This diurnal effect is so strong that the length of late morning NREM reports were similar to REM reports at the body temperature nadir ($t19=.45$, $p=.659$). The patterns of cortical activation supported by the active phase of REM-NREM and circadian cycles have both common and distinctive regions. For e.g., the active phase of the circadian, but not the REM-NREM cycle, activates the left temporal language regions. Research with much larger sample sizes will be necessary to describe how dream mentation produced by these different regions differs in its cognitive and affective properties.

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Within- and Between-Subjects Relationships of Waking Mood with Dream Emotional Tone in Nightmare Sufferers

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Introduction: Several researchers have proposed the possibility of a mood regulatory function for dreaming (e.g. Perlis & Nielsen, 1993). Kramer (1993) demonstrated a decrease in unhappy and anxiety mood subscales from night to morning in normal subjects and Cartwright et al (1998) found an improvement in morning mood when sleep is intact. However, depressed subjects have been shown to benefit from extended REM loss (Vogel et al. 1975) suggesting that they have higher levels of negative mood to regulate or that their sleep or dreams do not succeed in regulating mood. To investigate this model of dream function we assessed between- and within-subjects correlations of waking mood and overnight change in mood with dream emotional tone.

Methods: Nightmare sufferers (35 females and 11 males, mean age = 41.27 years (SD = 20.02) range 18-82) were recruited from the local population through advertisements. Participants kept a diary for 2 weeks in which they recorded their incidence of dreams and nightmares, and rated the emotional tone of these on a seven-point scale of very unpleasant (1) to very pleasant (7). Participants rated how anxious and depressed they were before sleep and on awakening using visual analog scales.

Results: Over the 2 weeks of the diary participants reported having a mean of 1.17 nightmares (SD= 1.09). Mean emotional tone (MET) of all the dreams and nightmares was 3.33 (SD= 0.94, range 1.43-6). Between-subjects correlations found that anxiety and depression before and after sleep were significantly correlated ($r = 0.903$; $p< 0.01$ and $r = 0.855$; $p < 0.01$ respectively). Anxiety before and after sleep were negatively correlated with MET of the dream ($r= -0.44$; $p= 0.002$; $r = -0.36$; $p= 0.017$ respectively). Similarly depression before and after sleep were both negatively correlated with MET($r= -0.418$; $p=0.004$ and $r = -0.296$; $p= 0.049$ respectively). Anxiety and depression were significantly higher before and after nightmares than dreams. However, of the 46 within-subjects correlations between anxiety before and after sleep just 6 were statistically significant, and 10 of the 41 within-subjects correlations between depression before and after sleep were significant. Of the 37 within-subject correlations between anxiety before sleep and MET of the dream, none were significant, and only 2 participants showed significant correlations between MET and anxiety after sleep. Two significant correlations were found between depression before sleep and MET and one between depression after sleep and MET. The change in anxiety and depression from night to morning was not significantly related to dream emotional tone in a between-subjects analyses, and within-subjects analyses revealed only 4 significant correlations between the change in both depression and anxiety and MET of the dream.

Conclusion: These findings are similar to those of Cellucci and Lawrence (1978; Journal of Clinical Psychology, 1978, 34: 721-725.) in that the within-subjects correlations of waking mood and dream emotional tone are rarely significant and usually very small. These results, and the non-significant correlations with mood change scores, oppose the mood regulatory function of sleep (although negative mood prior to sleep was associated with subsequent nightmares), whereas the higher between-subjects correlations support the simpler continuity hypothesis of dreaming.

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Staying Up Late Phase Delays The Human Circadian Clock

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Introduction: Late bedtimes coupled with early wake times for work are increasingly common in modern society. However the effect of adopting late versus early bedtimes on the human circadian clock has not been previously investigated.
Methods: Ten healthy subjects (5 m, 5 f) participated. Their self reported mean habitual weekday sleep schedule prior to participation was 22:50 ± 0.7 h to 7:00 ± 0.8 h. As part of a counterbalanced within subjects design, subjects participated in 7-19 nights with an early bedtime (22:00) and 7-19 nights with a late bedtime (1:00). In both conditions lights on was fixed at 7:00, and subjects were instructed to obtain at least 5 minutes of outdoor light between 7:00-8:00 every morning. All subjects slept at home in dark bedrooms during the scheduled times. Compliance with the sleep schedule and light/dark requirements was confirmed with a wrist actigraph and photosensor worn around the neck. On the final day in each condition, subjects participated in an overnight phase assessment session. Saliva samples were collected every 30 mins in dim light (<10 lux), and later assayed for melatonin. The dim light melatonin onset (DLMO) and offset (DLMOff), were determined as the points in time where melatonin concentrations crossed a threshold calculated as twice the mean of the first 3 low daytime points. The DLMO to DLMOff duration and area under the curve of each melatonin profile were also determined.
Results: Light data from the photosensors indicated that during the late bedtime nights, subjects were exposed to an average of approximately 40 lux between 22:00 and 1:00 (the individual averages ranged from 17 to 67 lux). During the early bedtime nights, subjects were in the dark from 22:00 to 1:00 and light levels were less than 1 lux. There was no difference in morning light exposure from 7:00 to 9:00 between the two conditions ($p>0.05$, average light exposure was 1024 lux). Following the early bedtime nights, the DLMO occurred at 20:08 ± 1.1 and the DLMOff at 6:49 ± 1.1. Following the late bedtime nights, the DLMO occurred at 20:46 ± 1.3 and the DLMOff at 7:18 ± 1.4. Thus, after the late bedtime nights the DLMO was delayed by 0.6 ± 0.3 h ($p<0.05$) and the DLMOff was delayed by 0.5 ± 0.6 h ($p<0.05$). The DLMO to DLMOff duration and area under the curve were not significantly different between the two conditions ($p>0.05$).
Conclusion: These results show for the first time that people who truncate their sleep by delaying their bedtime significantly phase delay their circadian clock even when the same wake up lights on time is maintained. Conversely, when people go to bed early they phase advance their circadian clock. This phase delay, or phase advance, is most likely due to the difference in light exposure in the evening (dim indoor room light versus dark). Thus, even when humans experience a typical 24 hour light/dark cycle, including bright outdoor morning light, the human circadian system remains sensitive to ordinary dim indoor evening room light.

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The Effect of Blocking Low Wavelength Light on Melatonin Production: Possible Prevention of Increased Cancer Risk in Shift-Workers

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Introduction: Suppression of melatonin production is common among shift-workers who spend nighttime hours under environmental lighting. Melatonin deficits caused by light has been recently linked with increased risk of breast and colorectal cancers. The influence of light on melatonin varies with wavelengths, with light of relatively short wavelength (between 470 to 525 nm) eliciting a significant suppression of nocturnal melatonin. Therefore, blocking light of low wavelengths in bright light conditions may prevent the suppression of melatonin. For this purpose we have designed optical filter lenses allowing selective exclusion of all wavelengths below 530nm while maintaining relatively good color recognition and a visual light transmittance. Our hypothesis was that wearing such light-filtering lenses could potentially prevent the nocturnal suppression of melatonin during shift-work in bright lighting conditions.
Methods: A total of 8 healthy young males (mean age 22.5+/-1.5) completed the study. All subjects underwent a psychiatric and sleep assessment to rule out significant psychopathology and sleep disruption. During the study, subjects were asked to stay awake overnight at the Sleep Research Laboratory for 3 non-consecutive nights over a two-week period. The first night, melatonin production measured (in saliva) under dim light (<5 lx) conditions established each individual's circadian profile of melatonin secretion, unaffected by light exposure. One week later the subjects were randomly assigned to wear the yellow filter lenses on either the second or third night. On the alternate night, the subjects were exposed to the bright light without wearing goggles. On all nights, 13 saliva samples were collected at regular one-hour intervals beginning at 8:00pm. On the second and third nights the subjects were placed in a well lit room (800 lx) designed to mimic a shift-work environment. The exact luminescence of the rooms was determined using a luxmeter. Due to individual variability in Dim Light Melatonin Onset (DLMO) and acute phase shifting effects of light on melatonin secretion profiles, we converted clock time to circadian time (CT). For this purpose, we referenced the beginning of melatonin production by designating the baseline DLMO as CT 14.
Results: All subjects wearing yellow lenses exhibited a melatonin secretion profile similar to their dim light pattern throughout the night. In contrast, bright light drastically suppressed melatonin production. Exposure to bright light and filtered light caused a phase delay in endogenous melatonin secretion, although the latter condition induced a less pronounced shift. Analysis of variance showed that suppression of melatonin levels at all data collection points (except at Pre-DLMO) did not occur when yellow lenses were worn (Pre- DLMO $t=1.32$, $p=.23$; CT14 $t=3.46$, $p=.01$; CT15 $t=3.94$, $p<.006$; CT16 $t=4.74$, $p=.002$; CT17 $t=4.16$, $p=.004$; CT18 $t=5.01$, $p=.002$; CT 19 $t=7.86$, $p=.0005$; CT20 $t=6.22$, $p=.0005$).
Conclusion: The strategy of protecting shift workers from melatonin deficiencies by simply preventing light of low wavelength from reaching the retina may be a cost-effective and practical solution to this problem.

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Assessing the Effects of Melatonin Secretion on Driving Performance and Subjective Measures of Sleepiness, Alertness and Fatigue

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Introduction: Melatonin (MLT) is a key neurohormone that synchronizes circadian rhythms in humans. It has been found that exposure to light during regular sleep hours, specifically within the range between 446-484nm, results in significant suppression of MLT and an inevitable misalignment of circadian rhythms. With 25% of the modern day workforce consisting of night-shift workers who routinely spend night hours under bright light, cognitive and performance related effects of disturbing MLT production are becoming of increasing importance. In order to normalize MLT production to the higher levels usually observed in darkness, while being exposed to bright light, we have developed yellow filter lenses allowing selective removal of all wavelengths below 530nm. Through the use of a driving simulator, we have been able to examine the short-term cognitive and psychomotor effects of suppression and normalization of MLT.

Methods: Eighteen healthy adults (11M, 7F, mean age 24.4 +/-4.1) with valid drivers licenses were screened for significant medical or psychiatric disorders; concomitant use of sedating or stimulating substances was disallowed. On the first night, subjects were exposed to constant bright light (800 lux) from 20:00 to 08:00h the following morning. The subjects performed four intentionally soporific 30-minute driving simulations on the York Driving Simulator at three-hour intervals (21:00, 24:00, 03:00, 06:00h). One week later, the participants followed the exact same procedure; however this time wearing low-wavelength filtering goggles for the duration of the experiment. Objective measures of driving performance included mean lane accuracy/road position (RP), mean speed, mean speed deviation, mean reaction time (RT) to virtual wind gusts and off-road events ("crashes"). Subjective states of sleepiness, alertness and fatigue were serially measured at 2-hours intervals starting at 20:00h on each night of testing. General linear model was used for the analysis.

Results: The following mean performance measures were obtained for the light and goggle conditions respectively: Speed: 90.1km/h+/-10.8; 90.2hm/h +/-12.9; Speed Deviation: 1.46km/h+/-10.7; 1.57km/h+/-12.8; RT: 1.107 sec+/-0.592; 1.13 sec+/-0.504; RP: 29.0+/-4.55; 29.2+/-2.91; Crash Rate: 4.3+/-5.7; 3.5+/-4.5. For the light condition there were performance differences with respect to RP (F=5.1, p=.02, df=3) and crashes (F=5.5, p=0.02, df=3) with significantly more accurate road position and fewer crashes during the first two driving sessions compared to the subsequent trials. For the goggles condition no significant differences were found. Between conditions there were no any differences except for RT at 24:00h (p=0.02 df=17) with slightly faster reaction times found in the light condition. All subjective measures in both conditions showed significant fluctuations towards increased sleepiness and fatigue and decreased alertness throughout the trials (p=0.01, df=17). There were no between condition differences.

Conclusion: Driving performance data suggests that there are no immediate effects of high levels of MLT production due to removal low wavelength light as compared with performance levels observed under not filtered bright light condition. Normalization of MLT production while wearing goggles does not affect significantly subjective measures of sleepiness, alertness and fatigue.

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Driving Simulation Performance and EEG Monitoring of Cognitive Functioning Following Ambulatory Anesthesia

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Introduction: Outpatient anesthesia has grown rapidly over the past decade. The newer anesthetic agents lead to rapid recovery from anesthesia and prompt recovery of gross cognitive and psychomotor function. More subtle driving performance parameters, following the administration of new anesthetic agents, lack adequate testing. Currently, patients are advised to refrain from driving for a 24-hour period while recovering postoperatively from receiving an anesthetic. The objective of this study was to determine whether driving skills have returned to baseline levels within two to 24 hours after receiving a balanced general anesthetic for day-surgery.

Methods: Fourteen patient with valid drivers licenses (8 males and 6 females, aged 43.5+/-11.6) who were scheduled to undergoing left knee arthroscopic surgery participated in the study. Using the York Driving Simulator, subjects performed 30-minute driving simulations prior to a surgery (baseline), two hours and 24 hours after the surgery. During each session, individuals were monitored for occurrence of micro-sleep (MS) episodes (defined as occurrence of 15 to 30 seconds of any sleep stage by EEG/EMG/EOG criteria) and attention lapses - AL (defined as intrusion of alpha- or theta EEG activity lasting more than 3 seconds but less than 15 seconds). Measured driving performance variables included: mean lane accuracy/road position (RP), mean speed, mean speed deviation, mean reaction time (RT) to virtual wind gusts and off-road events (crashes).

Results: RP was found to show significant within-group variation (F=3.6, p=.04, df=2), with post hoc tests demonstrating better lane accuracy achieved 24 hours after the surgery [RP baseline/RP 24 (p = .05). It is noteworthy that patients demonstrated poor lane accuracy both at baseline and two hours after the surgery [RP baseline; RP 02:00 (p> .05)]. RT two hours after the surgery was significantly longer as compared with values obtained after 24 hours and at a baseline [F=7.0, p=.01, df=1.4 (RT baseline: 0.985sec+/-0.344-RT 02:00: 1.340sec+/-0.474; p=.01/ RT 24:00: 0.906sec+/-0.351-RT 02:00; p=.02)]. All other driving performance variables (mean speed, speed deviation, and off-road events) failed to exhibit any statistically significant diurnal variation. While the occurrence of MS did not differ at all times of driving simulations (F=2.7, df=2, p=.11), there was a significant within-group variation for the occurrence of AL episodes (F=13.4, df=2, p=.0001). Specifically, AL episodes were found to occur more often two hours after the surgery in comparison to baseline and 24 hours after the surgery procedure [AL baseline: 1.9+/-1.3; AL 02:00: 3.3+/-2.0 (p =.02)/AL24:00: 1.0+/-1.2; AL 02:00 (p = .0001)]. There was significantly higher amount of AL occurred at baseline as compared with AL rates 24 hours after the surgery.

Conclusion: Both driving simulation parameters and EEG-verified attention lapses showed compelling evidence of impaired psychomotor performance two hours after receiving an anesthetic but relative normalization by the 24 hour post-anesthetic period. Poor lane accuracy and frequent attention lapses observed at baseline can be attributed to anxiety and sleep deprivation prior to the surgery.

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Effects of Low-Wavelength Light on the Continuous Performance Test and Subjective Sleepiness, Alertness and Fatigue

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Introduction: The goal of this study was to evaluate the effect of the absence of low-wavelength (<530 nm) light on subjective sleepiness/alertness/fatigue and objective performance. Subjective parameters were measured using the Stanford Sleepiness Scale (SSS), 7-item Fatigue Scale (FS), 7-item Alertness Scale (AS), Fatigue/Sleepiness/Alertness Visual Analogue Scales (VAS-F/VAS-S/VAS-A), and the Toronto Hospital Alertness Test (THAT) questionnaires. Objective performance of the subjects was evaluated on the Continuous Performance Test (CPT), a measure of sustained attention, by examining both errors of omission (i.e. failing to respond to target) and commission (responding to target inappropriately) along with the subjects reaction time. High errors of omission and/or commission suggest poor task orientation while a slow reaction time coupled to such errors would indicate inattentiveness.

Methods: The study data was taken from a group of 19 subjects (11 male, 8 female, mean age 24.7+/-4.6 years) over two nights (20:00 to 08:00h). All subjects underwent two overnight studies. Half of the group was shielded from low-wavelength light (wearing specific goggles) the first night and the other half were exposed to normal lighting conditions (both at 800 lux). The second night the groups switched conditions. Both nights, the subjects completed the subjective questionnaires (at 2 hours intervals) and CPT (at 3 hours intervals) throughout the night. The general linear model was used for the statistical analysis of all parameters (using SPSS for Windows).

Results: There were no significant differences in performance or subjective scores between the two nights. The SSS showed a normal circadian variation, with the sleepiest time between 6 a.m. and 8 a.m. during both the filtered and normal lighting conditions ($F=37.7$, $p=0.0001$, $df=2.7$; $F=44.8$, $p=0.0001$, $df=3.3$, respectively). The same pattern was observed on the FS in both conditions ($F=38.3$, $p=0.0001$, $df=2.7$; $F=43.7$, $p=0.0001$, $df=3.4$, respectively). The worst level of alertness was observed in the same time interval on both nights ($F=30.8$, $p=0.0001$, $df=2.9$; $F=47.4$, $p=0.0001$, $df=3.8$, respectively). The THAT and the VAS had similar circadian profiles on both nights as well. Interestingly, none of the CPT parameters revealed significant circadian variations throughout both nights, except for reaction time slowing towards the morning hours under filtered light ($F=4.3$, $p<0.01$, $df=2.6$). However, reaction time did not significantly differ at any time interval between the two conditions.

Conclusion: Taken together, the analysis of both subjective and objective data shows that the subjects were not affected by the absence of low-wavelength light. The same level of attentiveness and psychomotor performance were observed in both the presence and absence of low-wavelength light. Despite the circadian variations observed on the subjective scales, the subjects were able to perform at the same level throughout both nights. This emphasizes the discrepancy between objective testing, self-awareness and its relevance to performance levels.

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Evening Naps and Caffeine as Countermeasures for Sleepiness During Night Shift: A Field Study

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Introduction: Caffeine and/or napping prior to the night shift improves alertness and sustained attention in a 4-night simulated shift protocol, with the combination of napping and caffeine being slightly better than either napping or caffeine alone. The effectiveness of these combined countermeasures was tested in a field study during actual night shift work.

Methods: Subjects (Ss) at 2 study sites participated in a 4-consecutive-night crossover study comparing 2 conditions: (1) evening nap prior to the night shift on the first 2 nights plus caffeine 300 mg on all 4 nights (NC), and (2) placebo without napping all 4 nights (P). Condition order was counterbalanced. Thirty-nine Ss complied with the protocol and completed both study arms (28 m, 11 f; mean age 33, range 20-54). Caffeine or placebo was taken at the start of each shift. Three times during each night (at start, midway, and end of shift) Ss completed a 15-minute psychomotor vigilance task (PVT), the Karolinska Sleepiness Scale (KSS), and the Profile of Mood States (POMS). Ss slept at home during their usual hours, kept a sleep diary, and were monitored actigraphically. ANOVAs with repeated measures for condition, night, and time of night were the primary statistical method. A reciprocal transformation was used for reaction time of the slowest 10% of PVT responses (RT10) and a square root transformation was applied to PVT lapses (i.e., reaction time > 500 msec). Because of technical problems complete actigraphy data are available for only 25 Ss.

Results: Actigraph-estimated total sleep times (ATST) during the 2 NC evening naps were 73 and 58 minutes. ATST for daytime sleep did not differ between conditions; mean ATST for days 1-3 were 276, 312, and 316 minutes for NC, and 298, 333, and 304 minutes for P. In contrast, Ss reported sleeping less following nights 1 and 2 in the NC condition compared to P ($p < .01$). RT10 worsened across nights 1-4 ($F(3,93)=17.5$, $p<.001$) and showed a condition by time interaction ($F(1,31)=8.7$, $p=.006$). For P only, RT10 worsened from shift start (2.54) to shift end (2.24). In addition, at shift end, P RT10 was worse (2.24) than NC RT10 (2.43; $p=.04$). PVT lapses also showed a condition by time interaction ($F(1,31)=5.0$, $p=.03$). Transformed lapse frequency increased from 3.56 at shift start to 4.44 at shift end for P with no change for NC during the night. Lapses were more frequent across nights 1-4 ($F(3,93)=15.5$, $p<.001$). Mean transformed numbers of lapses were 2.88, 3.73, 4.37, and 4.23 for NC nights 1-4, and 3.38, 3.94, 4.3, and 4.38 for P nights 1-4. Subjective sleepiness showed a condition by time interaction ($F(1,31)=13.0$, $p=.001$) with increased sleepiness at shift end during P compared to NC (KSS=6.3 vs 5.6, $p=.006$). There was no change in sleepiness ratings across nights 1-4.

Conclusion: This rare field study of night shift workers documented that: 1) performance and alertness declined late in the night shift, 2) alertness and performance did not improve across successive night shifts (as found in some laboratory simulations), 3) a combination of napping and caffeine had modest positive effects on performance and subjective sleepiness in the early morning hours, and 4) daytime sleep duration of night workers is frequently less than 5 hours.

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Lack of NPY Immunoreactivity in Light-Activated Intergeniculate Leaflet Neurons in Rats

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Introduction: Synchronization (entrainment) of circadian rhythms is mediated in mammals by both photic (retinal illumination) and non-photic (e.g., increased activity/arousal) cues. The photic entrainment pathway includes retinal projections to the hypothalamic suprachiasmatic nucleus (SCN) and to the intergeniculate leaflet (IGL) of the lateral geniculate area, which in turn projects to the SCN. IGL neurons containing neuropeptide Y (NPY) and projecting to the SCN are critical mediators of non-photic effects on the circadian system. The IGL also plays a role in photic entrainment, but the neurotransmitters involved are uncertain. The IGL contains cells immunoreactive for enkephalin and GABA, with GABA being colocalized with NPY in a subpopulation of cells, which also project to the SCN. The functions of peptides and transmitters in the IGL other than NPY are unknown. To investigate the roles of different classes of IGL cells in photic and non-photic entrainment, we have used juxtacellular recording/labeling methods to study single IGL neurons. Photically responsive neurons were recorded in the IGL of anesthetized rats and labeled with neurobiotin, followed by immunostaining for NPY.
Methods: Male, Sprague-Dawley rats (250-350 g) were anesthetized with urethane (2 g/kg body weight) and mounted in a stereotaxic instrument. Following surgical preparation, glass micropipettes filled with 2% neurobiotin in 0.5M sodium acetate were lowered to the region of the IGL and used to record single-cell, firing-rate responses to 60 sec presentations of binocular retinal illumination. Cells were classified as photically activated, suppressed or unresponsive and then were driven with anodal current through the micropipette (15-20 min) to label them with neurobiotin. Neurobiotin-filled neurons were visualized immunocytochemically using fluorescence microscopy by staining for Cy2-conjugated streptavidin, while NPY neurons were labeled with Cy3-conjugated secondary antibody. Confocal microscopy was used to identify neurons stained with Cy2, Cy3 or double-labeled with both fluorescent markers.
Results: Fifty-four photically responsive neurons were recorded in the lateral geniculate area, and 42 of these cells were successfully labeled with neurobiotin. Of these labeled cells, 30 were activated and 9 suppressed by retinal illumination, while 3 were not responsive. These cells were located primarily in the dorsal and ventral lateral geniculate nuclei and in the IGL. Of the 10 neurobiotin-labeled cells located in the NPY-immunoreactive region defining the IGL, 8 were activated by retinal illumination, 1 was suppressed and 1 was unresponsive. None of the cells recorded in the IGL (nor those outside the IGL) were double-labeled for NPY immunoreactivity, although many NPY-labeled cells were visible in the same sections. The somata of one activated and one unresponsive IGL neuron were demonstrated under high-power confocal imaging to contain a few small NPY-immunoreactive profiles. These appear to represent NPY-containing terminals projecting to these IGL neurons.
Conclusion: Too few photically suppressed or unresponsive neurons in the IGL have been studied to characterize them. Results to date indicate, however, that photically activated IGL neurons are not NPY immunoreactive, but some receive NPY projections. Current studies are attempting to identify their neurotransmitter phenotype(s).

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Diurnal Preference And The Phase Timings Of Ambient Illumination And Rest-Activity

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Introduction: Interest in the study of diurnal preferences dates back to the early 1900's, when investigators observed individual differences in diurnal rhythms. During the last three decades, the focus has been on the relationship between diurnal preferences and properties of biological circadian rhythms. Most of the scientific studies have used the morningness-eveningness questionnaire (MEQ), since it is the most reliable measure of inter-individual differences in diurnal preferences. In fact, it corresponds well with known biological markers (e.g., body temperature and melatonin onset) in both stable laboratory environment and in conditions where masking effects are not controlled. Little effort has been made to ascertain whether diurnal preference is related to circadian rhythm observed in the natural environment. The purpose of this study was to determine the degree of correlation between the MEQ and phase timings of rest-activity cycle and ambient illumination exposure.
Methods: Seventy older adults of representative race (Black: 59% and White: 41%) and gender (women: 73% and men: 27%) participated in a multifactorial study investigating relations of sociodemographic and clinical factors to circadian rhythm measures. Their average age was 68.27 ± 5.97 years. Participants completed baseline questionnaires, providing sociodenographic, subjective, and health data. At baseline, the MEQ was used to assess individual diurnal preference. The MEQ is a 19-item scale ascertaining habitual rising and bed times, preferred times of mental and physical performance and subjective alertness after rising and before going to bed. As proposed by Horne and Ostberg, it is divided into three sub-categories: morning-type (MT), neither-type (NT), and evening-type (ET). Participants who met study criteria wore an actigraph (Actiwatch-L) at home to monitor 24-hr ambient illumination and rest-activity for a week. Cosine analyses were performed on activity-rest and illumination (log-transformed) data, which provided phase timings for both data series. All data were entered into SPSS 10.0 for final analyses.
Results: The MEQ scores were normally distributed (mean = 60.76, SD = 9.01, and skewness = -.446), and were categorized as follows: ET = 3%, NT = 35%, and MT = 62%. To examine the relationships of MEQ scores to phase timings of rest-activity and daily illumination, partial correlations were used controlling for age, sex, BMI, health status, and sleep efficiency. Results showed direct and significant correlations of the phase timings of illumination and rest-activity to MEQ scores (r_p= 0.34, $p < 0.05$; $r_p = 0.38$, $p < 0.01$, respectively).
Conclusion: Previous data have shown an association between MEQ scores and circadian rhythm measures of body temperature (oral and rectal) and dim light melatonin onset. Our results indicate that individuals scoring high (e.g., MT) on the MEQ dimension are likely to have earlier acrophases of illumination and rest-activity in their natural environment. It is important to note this observation was independent of participant's age, gender, or race.

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Circadian Variation of C-Reactive Protein (CRP) Under Constant Routine Conditions

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Introduction: High circulating plasma levels of C-reactive protein (CRP) are reported to be a risk factor for cardiovascular disease. Few studies have assessed sleep-wakefulness variations in CRP levels and no study has assessed circadian variation in CRP levels under controlled laboratory conditions. The current study assessed circadian variation in CRP levels using a constant routine protocol.
Methods: Ten healthy women and twelve healthy men (28.3 ± 9.3 (SD) years) participated in an inpatient research protocol. Participants passed a rigorous health screening consisting of medical history, physical and psychological exams, blood and urine chemistries and electrocardiogram. None reported shift work for the past three years or transmeridian travel in the previous three months. Participants maintained a routine of 8 h of scheduled sleep for three weeks at home prior to laboratory procedures. Toxicology screens verified that participants were drug free upon admission to the laboratory. Lighting conditions were ˜3.0 lux in the angle of gaze for baseline day 1 and ˜150 lux on days 2-3. The baseline days and the maintenance of a strict schedule prior to admission were designed to reduce inter-individual variability in circadian phase and light exposure history prior to the constant routine. Sleep was scheduled for 8 h at habitual bedtimes for three initial baseline days. This was followed by a 40 h constant routine (constant wakefulness, posture, nutrition intake and dim light exposure [< 1.5 lux]). Melatonin was assayed using an 125I radioimmunoassay technique (Elias USA, Inc., Osceola,WI). Plasma CRP levels were determined using a high sensitivity ELISA (ALPCO, Windham, NH). Data were z-score transformed and interpolated to provide equal sampling times. Circadian phase was assessed by calculating the dim light melatonin onset (DLMO25%). The DLMO25% was assigned a phase of 0 degrees and CRP data were averaged into 30 degree circadian bins. Repeated measures ANOVA with Greenhouse-Geisser degree of freedom correction factors for sphericity were used to test for significant time of day affects across the 24 h day.
Results: A significant effect of time of day was observed for CRP levels [$F(11, 231)=2.91$, $p < 0.01$]. Circulating CRP levels were highest near melatonin onset, decreased across the biological night and increased across the biological day.
Conclusion: The current findings indicate that circulating levels of the acute phase protein CRP demonstrate circadian variation. Thus, the circadian clock or down stream effectors appear to influence CRP levels across the 24 h day.

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Addition of a Non-Photic Component to a Light-Based Mathematical Model of Circadian Rhythms Predicts Entrainment at Low Light Levels

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Introduction: As recently as 20 years ago, relatively bright light was thought to be required for entrainment of the non-24-hour circadian pacemaker to the 24-hour day. However, studies of totally blind individuals (equivalent to 0 lux input conditions) as well as experiments under very dim light (1.5 lux) have suggested that non-photic stimuli may contribute to entrainment of the human circadian system to different entrainment (T-cycle) schedules (Klerman et al., 1998, Wright et al., 2001). Simulations of our present light-based mathematical model of the human circadian system (Kronauer et al. 1999, 2000) fail to predict entrainment at 0 or 1.5 lux to different T-cycles under intrinsic circadian periods (tau) between 23.88 and 24.12 hours. Therefore, we incorporated a non-photic component into our present light-based model to improve predictions of entrainment at low light levels.
Methods: We amended our mathematical model of the effect of light on the human circadian pacemaker to include a non-photic drive that enters the pacemaker independently from the light input. The non-photic component was modeled as a square wave reflecting the sleep-wake schedule and modulated by one of the state variables, x, in the circadian pacemaker equations. To test the predictions of the model to different T-cycles at 1.5 lux, we simulated the protocol described in Wright et. al. 2001. In that report, 5/6 individuals entrained to a 24.0 hour T-cycle, but 0/3 entrained to a 23.5 hour T-cycle and 0/6 to a 24.6 h T-cycle. We also simulated results from a 23.8 hour T-cycle schedule of a blind person with a tau of 24.1 hours. For each simulation, we used the subject's measured tau as the input to our model. To determine entrainment in our simulations, we calculated a phase angle between the circadian marker and the scheduled waketime. Subjects were classified as entrained if the change in phase angle were less than 0.001 hours for three or more consecutive cycles.
Results: Using the original light-based model, no individuals entrained to any of the T-cycles. With the addition of the non-photic component, entrainment occurred in the subjects for whom entrainment was seen experimentally. For the sighted subjects, 5/6 entrained to 24.0 hour and none to 23.5 hour or to 24.6 hour cycles. For the blind subject, consistent with the Klerman et. al. 1998 report, the final phase relationship between the circadian phase marker and the sleep-wake schedule was the same at the end of the T=23.8 hour portion of the protocol as at the beginning, when the subject was entrained to T=24.0 hours.
Conclusion: The addition of a non-photic component to our model allows predictions of entrainment at low light levels. These results suggest that a strict sleep-wake cycle with its associated behaviors (e.g., meals, social contacts, exercise, posture changes) may provide a non-photic stimulus to the circadian pacemaker. Although light remains the primary synchronizer of the circadian pacemaker, non-photic stimuli may significantly affect the circadian pacemaker under certain conditions. This finding needs to be tested with additional data sets.

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Determination of Endogenous Pacemaker Period May be Affected by Circadian Asymmetry In Human Photic Sensitivity

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Introduction: The forced desynchrony protocol (FD) has been a useful tool in appraising the human endogenous pacemaker period, τ, by suppressing the entraining effects of an unavoidable cyclic photic environment. By requiring the period of the imposed light/dark cycle, T, to be

far removed from τ, it is expected that the endogenous rhythm will free-run at τ. Simulations of FD were performed (Klerman et. al. 1996) using a light-based mathematical model (Kronauer, 1990) in which the circadian pacemaker was represented by a van der Pol oscillator and the action of light included both a nonlinear intensity function and a circadian variation of photic sensitivity symmetric about the circadian nadir. These simulations showed light-induced modulations of the daily phase shifts of the pacemaker (as seen experimentally, Ritz-De Cecco, 2003) but when averaged over the "beat" cycle between T and τ, the intrinsic τ assigned to the pacemaker, τ0, was accurately revealed when $|T - \tau|$ was ~4 hours. Twice recently the model used in these simulations has undergone revisions (Jewett and Kronauer, 1998, Kronauer et. al. 1999, 2000). The latest model embodies asymmetric sensitivity towards the delay shift, and, through a ½ power nonlinearity to the light stimulus, a significant sensitivity at low light intensity (I, in lux). These revisions have prompted us to revisit the FD simulations to determine the effects of asymmetry on τ0 at low I.

Methods: We simulated the 20 hour (13.67h wake, 6.33h sleep) and 28 hour (18.67 wake, 9.33 sleep) FD with the most recent version of the light-based mathematical model of the human circadian pacemaker, using I = 0, 1.5, 10, 15 or 25 during wake and I = 0 during sleep. The daily circadian minimum was calculated from the model and a best fit line was found through these points to determine the τ - τ0 change for each I.

Results: For I > 0, the observed τ are significantly longer than the assigned intrinsic value, tau0. These increments, τ - τ0, are essentially independent of τ0 and for 0 ≤ I ≤ 25 are well represented by τ - τ0 = 0.046 I½ for T = 20 hours τ - τ0 = 0.052 I½ for T = 28 hours For I = 10, τ - τ0 are 0.15 and 0.16, respectively (9 and 10 minutes).

Conclusion: These simulations are based on a model constructed to reproduce phase shift experiments over a wide range of I. The preferential sensitivity in the delay-shift leads to the prediction that the τ observed in FD may be biased. The bias, while small, is comparable and in the same sense as the average deviation of τ from 24 hours that has been observed in experimental FD (Czeisler et. al., 1999). The mean τ0 in the adult population may be even closer to 24 hours than previously suspected. An experimental test of these predictions would be valuable, not only to obtain the best estimate of average τ0, but, by implication, to support or refute the applicability of sensitivity asymmetry at low I.

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Sleep Complaints and Work Shift

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Introduction: Little information exists regarding the prevalence of shift work sleep disorder (SWSD), which is characterized by complaints of insomnia and/or excessive sleepiness temporally associated with an atypical work shift. Data from the 2002 Sleep in America Poll conducted by the National Sleep Foundation provided an opportunity to examine sleep symptoms for individuals working on different work shifts.

Methods: The 2002 Sleep in America Poll includes a sample of 1,010 Americans >18 years selected to be nationally representative of people in US telephone households for age, gender and geographic region. Participants were contacted by telephone; 698 of whom provided information about their work shift and are included in the current study. Of these, 514 identified themselves as day shift workers (DS), 30 as evening (ES), 35 as night (NS), and 101 as rotating shift workers (RS). The percentages of males in the DS, ES, NS, RS groups were 54%, 47%, 80%, and 58%, respectively. The maximum sampling error of the data is estimated to be +/- 3.1%.

Results: Significantly more NS (74%, p<.05) reported having one or more symptoms of insomnia 'at least a few nights a week' as compared to DS (57%), with intermediate rates for ES (67%) and RS (64%). The percentage of each group reporting that their sleep quality was usually fair or poor was highest for RS (36%) as compared to the other groups (DS=24%, ES=23%, NS=31%; p<.05 for each). ES tended to have difficulty falling asleep 'at least a few times per week' more than other groups (37%, p<.1 vs DS, 21%; RS=32%, NS=31%). Significantly more RS (26%) reported having sleepiness that interferes with their daily activities 'at least a few days a week' as compared to both DS and ES (13% and 10% respectively, p<.05 for each); 14% of NS workers endorsed that item. Respondents rated how they felt on a typical day, using a 5-point scale (tired=1, full of energy=5). DS (19%), RS (22%) and NS (20%) were more likely to report feeling tired (rating of 1 or 2) than ES (3%; p<.05 for each).The majority of participants in all groups reported driving drowsy at least once in the last year. Of those driving drowsy, 40% DS, 56% ES, 38% NS, and 50% RS stopped driving at least once, due to sleepiness. Significantly more RS (26%) reported actually dozing off behind the wheel, compared to NS (11%); DS (21%) and ES (24%) did not differ from other groups p<.05 for each on this item.

Conclusion: Given the small sample sizes and lack of rigorous sampling and call-back methods, only tentative interpretations are warranted. It appears that the percentages of workers on NS and RS reporting problems about sleep or sleepiness differ only modestly from those on DS, and those on ES overall have lower complaint rates than DS. Thus, it seems likely that individual differences in sleep-wake physiology, social situations, shift timing and other factors affect the likelihood of sleep/wake complaints in shift workers, and thus the prevalence of SWSD.

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Adjusting Process C of the Two-Process Model in Response to Light

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Introduction: The two-process model of sleep regulation, which consists of a homeostatic process S and a circadian process C, successfully predicts sleep timing and duration in a variety of experimental scenarios. The published equation of process C reflects a static process that, unlike the actual circadian pacemaker, cannot shift phase or change amplitude in response to light. This limits the use of the two-process model to experiments in which circadian rhythmicity is either known or assumed to be stable. Consequently, relevant operational scenarios like shiftwork cannot be readily modeled. This restriction can be overcome with the limit cycle oscillator model for the circadian pacemaker, which has a provision for light input as part of the differential equations that drive it. However, even under stable entrained circumstances with approximately 8 hours daily sleep, substituting the limit cycle oscillator in lieu of process C does not properly integrate the two models, for the limit cycle oscillator has a different phase, amplitude, and shape than process C. We derived a transformation that can morph the limit cycle oscillator into the profile of process C, so that the limit cycle oscillator can be employed as a component of the two-process model to improve predictions of sleep

timing and duration when the circadian pacemaker changes dynamically.
Methods: First we ran a 22-day simulation with the limit cycle oscillator model, starting at midnight and taking steps of 0.01 hours, using the Runge-Kutta method for numerically solving differential equations. For every simulation day, we implemented 8-hour sleep periods with 0 lux of light input (midnight to 08:00), and 16-hour wake periods with 150 lux of light exposure (08:00 to midnight). We sampled the predictions for the oscillator state variables x and xc from the last 2 days of the simulation, at intervals of 0.1 hours. We then calculated amplitude $A=\sqrt{(x2+xc2)}$ and phase $\varphi=atan(xc/x)$ across all time points. The transformation equation was posited as $C=A\Sigma k\beta ksin[k(\varphi+\Delta\varphi)]$, where k=1,...,m denotes the harmonics in the oscillatory profile, and C is the value of process C as per the published equation. Using non-linear multiple regression, we estimated the parameters βk and $\Delta\varphi$ for up to 6 harmonics (m=1,...,6).
Results: Evaluated by explained variance, the optimal transformation equation was found to contain m=5 harmonics (just like process C). The parameter values were $\beta1=0.1065$, $\beta2=-0.0243$, $\beta3=0.0100$, $\beta4=-0.0029$, $\beta5=-0.0013$, and $\Delta\varphi=0.8731$. This transformation of the limit cycle oscillator captured 99.4% of the variance in process C.
Conclusion: We successfully replaced process C of the two-process model of sleep regulation by the limit cycle oscillator model, offering flexibility of circadian phase and amplitude adjustment to the two-proces model in response to light without adversely affecting the model under normal, steady state conditions. This modification to the two-process model may expand its range of applicability to situation of, for instance, shift work and jet lag. The predictive potential of the modified model is investigated in a companion abstract (Xiao et al.).

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Intrinsic Circadian Period and Phase Angle Influence Daytime Sleep Tendency in Adolescents

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Introduction: Carskadon and Acebo (Sleep, 2002) proposed the hypothesis that entrained phase angle of sleep-wake to the circadian timing system influences the pattern of daytime sleep tendency in well-slept individuals. Further, data acquired in adults indicate that intrinsic period affects entrained phase angle, such that longer period predicts smaller phase angle of wake time to minimum core temperature or midpoint of melatonin secretion. We have tested these predictions in adolescents.
Methods: Participants were 24 healthy adolescents (Tanner stages 1 to 5; ages 9.6 to 15.2; mean = 12.9 years; 14 girls) who slept at home for at least 10 days on a fixed schedule (bedtime = 2130 (n = 3) or 2200; risetime = 0730 (n = 3) or 0800) confirmed by actigraphy and diary. They then began a 3-week in-lab assessment of intrinsic period using a 28-hour forced desynchrony protocol over 12 cycles. The following variables were determined for individuals. Midmelatonin phase was computed from salivary melatonin values collected at 30-minute intervals during a constant routine at the beginning of the in-lab session using a threshold of 4 pg/ml for onset and offset. Intrinsic period was computed by linear regression through melatonin onset phases measured across forced desynchrony cycles. Multiple sleep latency tests were administered every two hours during the constant routine beginning at 1030. The first 7 sleep latencies collected at the beginning of the constant routine were plotted and assigned a category (1-4) by one investigator (MAC) based on patterns of sleep latency values consistent with the aforementioned model's predictions, blind to all other data. Thus, for example, the MSLT pattern assigned category 4 showed maximal scores until tests 6 or 7, as predicted by a broad phase angle; the category 1 pattern had a "dip" (shorter latency) at the third test, as predicted by a narrow phase angle.
Results: Midmelatonin phase ranged from 0046 to 0412 (mean = 0225, sd = 44 minutes); intrinsic period ranged from 24.03 to 24.59 hours (mean = 24.25, sd = .16); phase angle of midmelatonin to entrained rise time ranged from 3.8 to 7.23 hours (mean = 5.56, sd = .72). Correlations of phase angle, intrinsic period, and sleep latency category score were performed and evaluated with one-tailed tests. The correlation between phase angle and sleep latency category score was statistically significant ($r = .39$, $p = .03$). Intrinsic period and sleep latency category score were also significantly correlated ($r = -.59$, $p = .006$), as were phase angle and intrinsic period ($r = -.81$, $p < .001$).
Conclusion: These data confirm that intrinsic period is a strong predictor of the entrained phase angle of sleep-wake to the circadian timing system in adolescents. Further, these findings support the hypothesis that phase angle has an influence on daytime sleep tendency patterns in well-slept adolescents. Thus, the MSLT pattern depends upon the alignment of the homeostatic drive for sleep that accumulates while awake with respect to the phase of the clock-dependent alerting signal provided by the circadian timing system.

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A Convergence Algorithm for Objective Determination of Dim Light Melatonin Onset (DLMO)

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Introduction: It has been proposed that dim light melatonin onset (DLMO) may be used to assess whether individuals with or without specific medical conditions (e.g., insomnia) or who undergo specific experimental challenges (e.g., partial or total sleep deprivation with or without countermeasures (e.g., naps or pharmaceutical agents)) have altered circadian phase. In such cases, it is necessary to have objective and robust determinations of phase angle in order to eliminate bias when making group comparisons. A number of alternative decision rules for identifying DLMO from melatonin response curves have been proposed. Previously, we developed a novel convergence algorithm that utilized four different rules to achieve consensus. This algorithm was originally developed for use in our case control study of risk factors for insomnia among elderly, community residing, cognitively intact, non-depressed individuals. In this present study, we now apply the convergence algorithm to identify DLMO over 4 separate days in 6 protocols involving partial and total sleep deprivation with various nap and pharmaceutical countermeasures.
Methods: In the insomnia case control study, serum melatonin (assessed by Melatonin Direct I-125 RIA, IBL Laboratories, Germany) was collected every 0.5 hr from 18:00 to 24:00, at 1:00, 2:00, 3:00, and 4:00, and then every 0.5 hr until 8:00. Baseline was defined as mean over 18:00, 18:30, and 19:00. In the sleep deprivation protocols, serum melatonin (assessed by Bühlmann Melatonin RIA) was collected from noon to 10:30am the next day, every 1.5 hrs. In both cases, baseline was defined as the mean of the first 3 measures. The algorithm determines three points: the 1st time point at which measurable melatonin is 100% greater than the mean of the proceeding 3 values; 10 pg/ml in absolute

value while the mean of the next 3 observations also exceeds 10 pg/ml; and 100% of baseline. These values are used to determine an initial consensus according to specified criteria. If no initial consensus is reached, an extended consensus rule is employed that includes evaluating the first time that concentration exceeds baseline + 2 times baseline SD. When applied to data arising from the deprivation protocols, the original algorithm had to be modified to accommodate the less frequent sampling rate.
Results: The algorithm produced a consensus DLMO determination for 150 of 180 (83.3%) elderly cases and controls with another 11 determined by a blinded adjudication process. When subsequently applied to 68 healthy, non-elderly subjects contributing 272 melatonin profiles, a consensus DMLO determination was achieved 262 (96.3%) times. Mixed model ANOVA was used to estimate intra-class correlations (ICC) controlling for day and protocol in order to assess day to day reliability. ICC values ranged from 0.96 to 0.15 with an overall ICC equal to 0.51. ICC values were low in some cases as a consequence of the coarse sampling rate.
Conclusion: The use of multiple criteria in an objective consensus building algorithm has utility in enhancing objectivity in DLMO comparisons among experimental groups.

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Does Effort Follow a Circadian Rhythm?

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Introduction: Reaction time, vigilance and mood show circadian rhythmicity and are negatively affected by sleep loss. Sleep loss also negatively impacts objectively measured effort. This study sought to determine whether there is circadian variation in effort.
Methods: Twenty male and 31 female undergraduate students (mean age 20.78 years, SD=4.84, range=18 to 42) completed the assessment on three separate occasions over a five-day period and each session was held at a different time of day (e.g., 9AM, 12PM or 6PM). The assessment included two objective effort measures; a non-academic task choice question and the Math Effort Task (MET). A subjective effort question asked participants to rate the effort they applied to the previous task. Also included were the Stanford Sleepiness Scale, the Profile of Mood States, oral temperature and a simple reaction time task.
Results: A repeated-measures ANOVA examining time-of-day effects on task choice indicated that the most difficult non-academic tasks were chosen at 9am (M=2.29), and then at 6pm (M=1.71), while the simplest tasks were chosen at 12pm (M=1.65),[F(2,100)=6.975,p=.001]. A similar ANOVA for math difficulty was not significant. However, a paired t-test showed that the math problems selected at 9am (M=2.68) were more difficult than those selected at 6pm (M=2.35), thereby corroborating the task selection results [t(50)=2.333,p=.024]. Further analyses indicated that the task choice and math difficulty level selections were not a function of the order of sessions. Additional repeated-measures ANOVAs looking at time-of-day effects were computed. There was a significant body temperature effect such that temperature was highest at 6pm (M=97.91), followed by 9am (M=97.52) and 12pm (M=97.45), [F(2,100)=3.210,p=.045]. Vigor and fatigue also varied significantly. Vigor peaked at 12pm (M=13.00) and was lowest at 9am (M=10.24), [F(2,100)=4.058, p=.020] while fatigue was lowest at 12pm (M=6.00) and highest at 6pm (M=7.07), [F(2,100)=4.531, p=.032]. Performance accuracy and sleepiness did not vary with time of day.
Conclusion: Effort, as evaluated by two objective measures, was greatest at 9am and was not consistent with vigor or body temperature trends. Performance accuracy remained unchanged throughout the day. A compensatory control of mental processes model is applied to explain the variations in effort. At 9am, participants may have more reserve effort but by 6pm the reserve may be depleted. Further analyses will evaluate the contribution of sleep factors to objective and subjective effort.

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Circadian Adaptation During Chronic Sleep Restriction at Different Circadian Phases

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Introduction: Behaviorally mediated alterations of sleep-wake timing can affect endogenous circadian rhythmicity. Circadian adaptation to new sleep-wake schedules depends on light:dark exposure, timing and duration of sleep, and potentially sleep loss incurred during schedule changes. This experiment investigated circadian adaptation following systematic alterations in the timing and duration of sleep.
Methods: As part of a larger study, n=63 healthy subjects (38m, 25f; aged 21-45y) completed a 15-day experiment. Following one baseline night (23:30-07:30), subjects were assigned to a morning or afternoon sleep protocol. In the morning protocol, subjects remained awake for 20h, followed by 8h TIB (03:30-11:30). In the afternoon protocol, subjects remained awake for 28h, followed by 8h TIB (11:30-19:30). Subjects were then randomized to 4h, 6h or 8h TIB for 10 days. In the morning conditions, all restricted sleep periods terminated at 11:30; in the afternoon conditions, all restricted sleep periods terminated at 19:30. Every condition ended with two nocturnal recovery sleep periods (23:30-09:30). Subjects remained in the laboratory throughout, with fixed light levels (<50lx during waking; <1lx during sleep periods) and ambient temperature (24±1°C). Rectal temperature was measured at 6min intervals to assess circadian rhythmicity. Phase changes were estimated using Lomb-Scargle periodogram analysis. For the first detected near-24h peak in each subject, we recorded the deviation from 24h as the subject's apparent average daily phase shift. Since sleep influences body temperature, we also estimated the effect of the placement of the sleep periods by performing periodogram analysis on the corresponding step functions.
Results: Subjects in the 4h, 6h and 8h morning sleep conditions appeared to shift 0.01±0.27h, 0.11±0.18h and 0.05±0.21h per day (mean±s.d.), respectively. Subjects in the 4h, 6h and 8h afternoon sleep conditions appeared to shift 0.01±0.27h, 0.39±0.48h and 0.62±0.69h per day. There was a significant increase in the magnitude of phase shift with increasing sleep duration (F[2,57]=4.03, P=0.023) and with the later timing of sleep (F[1,57]=7.46, P=0.008), but the interaction of duration by timing was not significant (F[2,57]=2.65, P=0.079). For the 4h, 6h and 8h morning sleep conditions, the average daily shifts in the temperature profile attributable to the occurrence of sleep were estimated to be -0.26h, -0.20h and -0.20h, respectively. For the 4h, 6h and 8h afternoon sleep conditions, the average daily shifts attributable to sleep were estimated to be 0.98h, 0.85h and -0.57h per day.
Conclusion: These results suggest that the magnitude of circadian phase shifts depended on the placement and duration of the chronically restricted sleep periods, albeit with large inter-individual differences. The apparent phase shifts must be interpreted in the context of masking effects from sleep, however, which resulted in rhythmic changes in body

temperature that cannot readily be distinguished reliably from the endogenous circadian rhythmicity. Further investigations will use purification techniques to separate the masking effects of sleep from the endogenous changes of circadian phase.

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Predicting the Duration of Chronically Delayed Sleep

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Introduction: The two-process model of sleep regulation successfully predicts sleep duration in various scenarios with normal entrainment, but its circadian process C cannot adapt to changes in sleep-wake schedules and light exposure. Kronauer and others have overcome this limitation with the limit cycle circadian oscillator model, which we incorporated in the two-process model by means of a transformation derived in a companion abstract (Amin et al.). Here we report on a preliminary investigation of whether this modification of the two-process model leads to improved predictions of sleep duration in a study of delayed bedtimes.
Methods: As part of a larger project, 2 subjects (1 male, 1 female; both age 23) were studied under standardized laboratory conditions. After one day with 8h time in bed (TIB) for baseline sleep (23:30-07:30), they were kept awake for 20h to delay their bedtimes. They were then allowed 8h delayed TIB (03:30-11:30) for eleven consecutive days. Finally, they had two days with 10h TIB for recovery sleep (23:30-09:30). Polysomnographic recordings were made for all baseline and recovery sleep periods, and for two out of every three delayed sleep periods. Sleep records were scored using conventional criteria to assess total sleep time (TST). Light exposure was no more than 50 lux during scheduled wakefulness and approximately 0 lux during scheduled sleep. Model simulations of sleep and wakefulness in this study protocol were run with the original two-process model (i.e., published equations) and with the modified two-process model (see abstract by Amin et al.). For the latter, light exposures of 0/50 lux were assumed during scheduled sleep/wakefulness. We extracted the different model predictions of sleep duration for all recorded sleep periods.
Results: The original two-process model predicted a rapid stabilization (within two days) of sleep duration to 5.5h across the delayed sleep periods, while the modified two-process model predicted a steady increase of sleep duration from 5.8h to 7.4h as the circadian component of the model adapted to the delayed schedule. We compared the predictions of the two model versions to the actual TST observations by computing the mean squared error (MSE) across the recorded sleep periods. The MSE for the original model was 2.10, while the MSE for the modified model was 1.34 (smaller is better). For comparison, had we assumed that TST was equal to TIB as an operational definition of negligible accuracy, then the MSE would have been 4.02; and had we been able to predict TST as averaged over the two subjects with perfect accuracy, then the MSE would have dropped to 0.75.
Conclusion: The observed MSE values imply that on the range of the MSE scale (i.e., 0.75-4.02), we achieved an improvement from 58.7% to 82.0% accuracy by replacing process C with the limit cycle circadian oscillator. While conclusions from this finding are limited by the small number of subjects, it suggests that our modification of the two-process model may be viable and ready for validation in a larger study.

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Circadian Sleep Phase Preference And Sleep Patterns In Adolescents

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Introduction: Circadian sleep phase preferences (morningness/eveningness) are known to vary with age, sleep/wake patterns, biological rhythms, and behaviors. However, there have been inconsistent findings concerning circadian preference and sleep need. The present study evaluates the relationships among Morning/Evening types and sleep patterns (such as sleepiness, subjective estimation of sleep need, sleep debt, depression) in Korean adolescents.
Methods: A school Sleep Habits Survey (a modified version of Carskadon's survey) was administered to 555 Korean students (male 52.9%, female 47.1%)ranging from 5 to 8 graders (mean ages 10-13) who were selected by 2-way stratification sampling method. The survey included items regarding sleep/wake patterns as well as various scales including Morningness/eveningness Scale, Daytime Sleepiness Scale, Sleep/wake Problems Behavior Scale and Depressed Mood Scale.
Results: The M/E scores from 555 students ranged from 12 to 42 (with higher scores indicative of greater morningness), and the mean was 25.10(sd=3.93). The scores differ neither between males and females nor among the 5-8 graders. M/E types were identified by 10-90 percentile split of the scale: E-types(12-21: M=18.65: n=71) and M-types(33-42: M=31.34: n=77). For M-types and E-types, on weekdays(on weekends), mean bedtimes were 0:18am (11:58pm) and 00:52am.(00:59am), mean wake-up times were 06:15am.(08:18am), 06:3 8am.(10:28am). Compared to M-types, E-types reported later bedtimes both on weekdays ($p<.01$) and weekends ($p<.001$), and later wake-up times both on weekdays ($p<.001$) and weekends ($p<.001$). While the TIBs (time in bed) were not different for M-types and E-types on weekdays, E-types' TIB was longer than M-types' on weekends ($p<.001$). Oversleep on weekends (compared to weekdays) was more for E-types ($p<.001$). Sleep latency for E-types (M=30 min) was longer than that for M-types (M=19 min) on weekdays($p<.05$), but not on weekends. Sleep need (subjective ideal sleep time) was longer for E-types (M=493 min) than for M-types (X=449 min) ($p<.05$). With the same amount of sleep on weekdays, E-types' daily sleep debt (subjective ideal sleep need minus weekday TIB) (M=146 min) was also greater than M-types' (M=93 min) ($p<=.01$). On weekends, sleep debts for both M-types (M=-50 min) and E-types (M=-75) were minus which meant they slept more than their ideal sleep need. The degree of E-types' minus sleep debt was larger than that of M-types ($p<=.0001$). Regarding sleep problems, E-types, compared to M-types, showed higher scores on the Sleep/Wake Behaviour Scale ($p<.0001$), indicative of more problems such as sleep onset insomnia, night awakenings, subjective poor sleep quality. E-types also reported more subjective daytime sleepiness by showing higher scores on the sleepiness scale ($p<. 0001$). Furthermore, E-types seemed to have more emotional problems by showing higher scores on the Depressed Mood Scale, compared to M-types ($P<.05$).
Conclusion: In the present study, E-types, compared to M-types, showed greater sleepiness despite the same TIB(time in bed) on weekdays and even more TIB on weekends, and E-types also showed greater sleep need and greater sleep debt. The present finding may be explained, at least in part, in relation with the delayed phase of their circadian sleep rhythm. On weekdays, by forcing them to go to bed earlier in their

delayed circadian rhythm, E-types' sleep latency is longer resulting in subjective feeling of insufficient sleep. By showing that E-types were more depressed and had more sleep/wake behavior problems, the present findings suggest that morningness/eveningness is correlated to not only sleep patterns but also many other psychological variables. Therefore, circadian sleep phase reference should be considered in evaluating adolescents' emotional/behavioral aspects. It needs to be explored in further detail how circadian preference, sleep behaviors, sleep need and other emotional/cognitive factors are related.

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Comparison of Melatonin Suppression by Blue Wavelength Light in Young and Older Adults

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Introduction: Recent data from young subjects indicates that light in the blue wavelength region is the most potent for the circadian timing system. However, aging decreases the transmission of shorter (blue) wavelengths through the lens. In addition, degeneration of the blue-sensitive melanopsin-containing ganglion cells occurs with age. The functional impact of these age-related changes on the circadian system is not known. This study used the model of light-induced suppression of melatonin to assess the responsiveness of the aging circadian clock to different wavelengths of light.
Methods: To date, six healthy young adults (6 F, 26.5 ± 2.5 years) and 3 healthy older adults (2F, 1M, 70.0 ± 4.0 years) completed 4 overnight stays in the Clinical Research Center. Each admission was separated by at least one week. At each stay, subjects were exposed to a specific light condition for 90 minutes in a randomized order. Light exposure began at midnight in older adults and at 1:00 am in young adults, times that target melatonin synthesis at the plateau of the melatonin profile. The 4 different light conditions were control (with glasses not turned on), blue (464nm, λfull = 50nm), green (520 nm, λfull = 66nm), or red (640 nm, λfull = 54nm) wavelength regions. Subjects wore specially designed glasses that delivered light via optical fibers (Somnavue, Enlightened Technologies Associates). Each wavelength of light was matched for photon density (2.7 × 1013 photons/cm2/s). Blood samples were taken at baseline and every 30 minutes during light exposure to determine the magnitude of melatonin suppression following exposure to light. The percent suppression of melatonin at 90 minutes was compared in the young and older subjects by multi-factor ANOVA with repeated measures.
Results: Exposure to blue light in young subjects resulted in melatonin levels that were 44% ± 48.1 lower than the control night at the same time (90 minutes, p=0.07), whereas green and red wavelengths suppressed melatonin by only 14% ± 15.8 and 13% ± 32.1 respectively relative to control. In the three older subjects studied to date, melatonin levels following exposure to the blue wavelength light were 13% ± 2.2 lower than control, similar to green at 17% ± 16.9 suppression. Red wavelength light suppressed melatonin by only 5% ± 7.8 relative to control. Statistical comparison of melatonin suppression in young and older subjects will be conducted following completion of additional subjects.
Conclusion: These preliminary results suggest that aging may alter the responsiveness of the circadian system to blue light. Age-related changes in transmission of the shorter wavelengths and/or degeneration of melanopsin ganglion cells may be contributing factors. Therefore, the blue wavelength may not be more advantageous than full spectrum light for the treatment of circadian rhythm sleep disorders in older adults.

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Safety Goggles That Block Blue-Green Wavelengths Do Not Abolish Light-Induced Phase Shifts In Humans

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Introduction: Recent studies indicate that light in the blue wavelength region is the most potent for the circadian clock. Under certain conditions, such as morning travel home from a night shift, it may be advantageous to maintain visual light transmission while blocking photic resetting of the circadian clock. In the present experiment, we tested the effect of wearing safety goggles that selectively blocked transmission of either long or short wavelengths on light-induced phase shifts in humans.
Methods: Data is presented from 11 subjects (4 M, 7 F, 27 ± 4.5 years, 6 of whom participated in both conditions) who were admitted to the Clinical Research Center for 4 night/ 3 day stays under controlled conditions (< 20 lux, with 8 h sleep in dark) with blood sampled throughout baseline and post treatment nights. On night 3, subjects wore narrow spectrum laser safety goggles (Edmund Optics) during exposure to broad spectrum fluorescent lights (2 h, ending 2 h prior to Tmin). One filter blocked wavelengths less than about 560 nm (purple, blue, and green), and let through a relatively high intensity orange peak at 613 nm and a small secondary peak at 589 nm (total photon density 2.19 x 1015 photons/cm2/sec, about 2,300 lux at eye level). The other filter blocked wavelengths greater than about 560 nm, and let through relatively low intensity peaks in blue (488 nm) and green (547 nm) wavelengths (total photon density 4.12 x 1014 photons/cm2/sec, measuring about 500 lux). The magnitude of light-induced changes in the dim light melatonin onset (DLMO) was compared to results obtained from 15 subjects (8 M, 7 F, 29.4 ± 5.3 years) who had participated in both dim control (6.64 x 1013 photons/cm2/sec, or 25 lux) and bright (2.48 x 1015 photons/cm2/sec, about 3,000 lux) unfiltered broad spectrum white light studies.
Results: Exposure to broad spectrum bright light resulted in phase delays of the DLMO (-0.95 ± 0.71 h) that were greater than under control dim light (-0.03 ± 0.52 h, $p < 0.001$). Blocking transmission of blue/green wavelength light resulted in phase shifts (-0.51 ± 0.64 h, n = 9), approximately half the magnitude of bright broad spectrum light of similar illuminance, that were not statistically different from either the bright or the dim light conditions. In contrast, low intensity blue/green wavelength light resulted in phase delays (-0.82 ± 0.85 h, n = 8) similar to those obtained with bright white light, despite the lower illuminance (500 vs. 3,000 lux).
Conclusion: Exposure to low intensity blue/green wavelengths induced phase delays of similar magnitude to those obtained by bright broad spectrum light, while complete blockade of light in the blue/green wavelength region only partially reduced light-induced phase shifts of the circadian clock. These results support recent evidence that blue wavelength light is the most potent wavelength for the circadian clock, with longer wavelengths contributing to the phase shifting effects of light in humans. Filters that selectively block blue/green wavelength light may only partially protect against photic resetting of the circadian clock.

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Sleep Phase Delay Syndrome And Irregular Sleep Schedules Are Prevalent In Commercial Pilots

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Introduction: The lack of a life routine caused by schedules and work rhythm determine a series of consequences to commercial pilots such as: sedentarism, loosening of biological clock control, and sleep disorders that can bring serious damages on the activity and work performance of pilots. Objective. The aim of this study is to verify the Prevalence of Sleep disorders in Commercial Pilots.
Methods: We studied 104 commercial pilots working in national routes, 21 to 60 years of age (37.5±7yo), Ninety nine percent were male. The data were accessed by a sleep questionnaire, Epworth Sleepiness Scale (ESS), and Sleep Diary. Statistical Analysis. The data was analyzed with Descriptive Statistics.
Results: We observed that 13% presented BMI>30 and 58% presented neck circumference above 40cm. We have verified that 66% of the pilot had irregular schedule to sleep and wake up. They sleep between 8:00 PM and 3:00 AM, mean 10:30 PM (range: 8:30 PM to 00:30 AM) and wake up between 6:00 AM and 12:00 AM, mean 8:00 AM (range: 7:30 AM to 8:30 AM). In the Sleep Diary, 47 pilots presented a Total Sleep Time of 7h ±47min, divided in night sleep (1h±4min), early morning sleep (3:27h±9min), morning sleep (2h ±7min), and afternoon sleep (24min ±9min). We observed that 11% of the pilots presented sleep phase delay syndrome; 3% presented insomnia; 2% sleep breathing disorders; 2% narcolepsy symptoms; 2% restless leg syndrome symptoms; 2% parasomnia, detected daytime sleepiness in 34% of the pilots (ESS>12).
Conclusion: Sleep disorders were prevalent in commercial pilots, and the major findings in this study was the irregular schedules to sleep and wake up and a total lack of routine of these professionals causing sleep delay or insufficient sleep.

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Phase Shifting The Entrained Circadian Melatonin Rhythm In Humans: Effects Of The Calcium Channel Antagonist Nimodipine And A Single Pulse Of Light

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Introduction: Phototherapy currently used for the treatment of circadian rhythm disorders requires a significant time investment from the patient receiving treatment. Enhancement of light-induced phase changes in the circadian clock may encourage greater patient compliance when receiving phototherapy. We previously demonstrated that the calcium channel antagonist nimodipine potentiated light-induced melatonin suppression in humans and light-induced phase delays in mice. In the present study, we examined the effect of nimodipine on the magnitude of phase delays following a single pulse of light in humans studied under entrained conditions.
Methods: Ten subjects (4 M, 6 F, mean age ± SD: 30 ± 4.77) were admitted on three separate occasions to the Clinical Research Center. Each stay lasted 4 nights and 3 days in constant conditions (<20 lux, subjects remained semi-recumbent and received isocaloric meals). Subjects became habituated to the study conditions during the first night, and on the baseline (second) and post-treatment (fourth) nights blood was sampled from 16:00 until 10:00 the following morning. On the third night, subjects received one of three treatment conditions in a repeated measures design: 1) placebo and light, 2) nimodipine (30 mg, orally) and light, or 3) a control dim light condition with either nimodipine or placebo. The order of treatments was randomized. Treatments consisted of 3h of bright light administration (3,500 lux) or dim light control (<20 lux). Light exposure was centered 3h before the subject's Tmin as determined on the baseline night with scheduled sleep episodes for 4h before and 4h after treatment. Melatonin levels were measured with RIA and the magnitude of the phase shift was calculated as the difference between the baseline and post-treatment melatonin profiles (50% of maximum on the rising [onset] and declining [offset] phase).
Results: Nimodipine did not affect the timing of the clock, as measured by the circadian melatonin rhythm, under controlled dim light conditions. There was a slight delay drift of the melatonin profile in the combined (nimodipine and placebo) control condition (onset phase delay: -0.18 ± 0.83, offset phase delay: -0.46 ± 0.78). Exposure to bright light (3,500 lux for 3h) resulted in phase delays of the melatonin profile (onset phase delay: -1.17 ± 0.59, offset phase delay: -1.19 ± 0.83) that were greater than on the control night (onset: $p<0.01$, offset: $p<0.05$). Phase delays following treatment with nimodipine and light (onset phase delay: -0.97 ± 0.85, offset phase delay: -1.13 ± 0.46) were indistinguishable from those following treatment with placebo and light.
Conclusion: A single 3h pulse of bright light resulted in shifts of circadian melatonin rhythm that were approximately 1h greater than shifts following a control study under dim light. These results indicate that this protocol can be used to detect experimentally-induced changes of the circadian clock in subjects studied under regular sleep/wake schedules. In this protocol nimodipine had no effect on the magnitude of phase delays when administered prior to light treatment. These results contrast with the effects of nimodipine on light-induced suppression of melatonin in humans and phase shifts in mice. Factors that account for the lack of an effect of nimodipine on light induced phase shifts in the present study may include the near saturating light exposure and/or dose of nimodipine.

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Circadian and Homeostatic Components of Mathematical Models of Neurobehavioral Performance for the Effects of Low Dose Caffeine During a 42-Hour Forced Desynchrony Protocol

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Introduction: Mathematical models have been developed to predict neurobehavioral performance during extended wakefulness, sleep disruption, and circadian misalignment (e.g., Jewett & Kronauer JBR 1999). Most models do not include the effects of pharmacological countermeasures. In this abstract, we investigate the effects of extended low-dose caffeine on human neurobehavioral performance by studying circadian and homeostatic models derived from forced desynchrony data.
Methods: The analysis includes data from 16 subjects (8 placebo, 8 caffeine) studied on a 42.85-hr forced desynchrony (28.57-hr enforced wake, 14.28-hr scheduled sleep) protocol. Subjects were given placebo or 0.3mg/kg/hr caffeine every hour during all wake episodes of the forced desynchrony. Subject data, protocol details and circadian phase

assessment were previously reported (Wyatt et al., 2000). Neurobehavioral testing occurred multiple times throughout each wake episode. Cognitive Throughput as measured through the ADD test (ADD), Subjective Alertness (Alert), Digit Symbol Substitution Task (DSST), Karolinska Sleepiness Scale (KSS), and the Psychomotor Vigilance Task (PVT) collected during the forced desynchrony were averaged into 4.08-hour bins and then averaged across all subjects within a group. The homeostatic component (time-awake) of performance was fit to a linear, polynomial, and single or double time constant exponential functions. Since there were non-linear interactions between circadian phase and length of time awake, the data were analyzed for circadian influence at each 4.08-hr bin since awakening. For each bin, the amplitude of the circadian oscillation was fit to 1, 2, and 3 harmonic functions. The best-fit was chosen using the Akaikie Information Criterion. Matlab 6.5.1 (Mathworks, Natick, Massachusetts) was used to compute all function fits.

Results: For all subjective and objective measures except ADD, a 2-time-constant exponential was the best fit to the homeostatic component of neuro-behavioral performance; the ADD measure was best fit by a Gaussian. The data from the caffeine group could fit by the same functions as the data from the placebo group. There were differences in the mean and amplitude of fits between groups. Data from the caffeine group had longer time constants of the homeostatic fit for the objective but not subjective measures. The best-fit of the amplitude of the 24-hour component of the circadian rhythms in each subjective and objective measures was a single-time constant exponential fit, although the time constant was close to zero, resulting in a near-linear curve. For subjective measures, there was no difference in relative amplitude between caffeine and placebo groups across homeostatic bins. For objective measures (ADD, DSST, PVT) the circadian amplitude was smaller across all homeostatic bins for the caffeine group.

Conclusion: The fits to data from caffeine and placebo groups are different. Caffeine lowered the amplitude of the fit function of subjective measures of alertness. However, caffeine affects components of objective neurobehavioral performance reducing the amplitude of the circadian component of the function. The lack of correlation between subjective and objective measures of alertness is similar to that seen in non-pharmacological studies. These descriptive mathematical models are a productive step in constructing interactive models for predicting the effect of caffeine on performance during a variety of sleep-wake schedules.

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Predicting Melatonin Onset Phase in Adolescents on Summer and School Schedules

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Introduction: Previous studies have shown that habitual sleep/wake variables, especially rise time and midpoint of sleep, can predict the onset of melatonin in adults. This analysis examined whether sleep schedules are able to predict melatonin onset phase in adolescents while on school year or summer time schedules.

Methods: Forty-five adolescents (23 boys), mean age = 12.5 (sd = 1.4) years were studied on a summer schedule; a separate sample of 51 adolescents (24 boys), mean age = 11.3 (sd = 0.9) years was studied on a school-year schedule. Salivary melatonin was collected at 30-minute intervals in dim light (< 40 lux) on one evening. Melatonin onset was determined using linear interpolation with a 4 pg/mL threshold. All participants slept at home on a sleep schedule of their own choosing for a week before saliva collection. They called every morning to report the previous night's bedtime and wake time (from which midsleep was also derived), and these values were averaged for 5 nights before saliva collection. Within-group bivariate regressions were computed using bedtime, wake time, and midsleep to predict melatonin onset phase.

Results: Bedtime (2255 (sd = 58 min) vs. 2129 (sd = 32 min)), wake time (0807 (sd = 60 min) vs. 0643 (sd = 26 min)), midsleep time (0331 (sd = 53 min) vs. 0205 (sd = 23 min)), and melatonin onset phase (2130 (sd = 66 min) vs. 2025 (sd = 40 min)) were significantly later for the summer versus the school-year groups ($p < .0001$ for all). Correlation coefficients for melatonin phase versus all 3 sleep variables in the summer group were statistically significant ($p < .0001$ for all), though the correlations were significantly greater for wake time ($r = .78$) and midsleep ($r = .76$) than for bedtime ($r = .58$). For the school-year group, correlation coefficients for bedtime ($r = .51$) and midsleep ($r = .49$) were statistically significant, whereas wake time ($r = .25$) was not. The regression equation for the summer group using waketime (predicted melatonin onset phase = .86 x summer waketime + 14.55) was able to predict melatonin onset phase within a 2 h and 51 min window for that group.

Conclusion: As in adults, self-selected sleep schedules in which sleep is less constrained (i.e., the summer schedule group) resulted in a better ability to predict melatonin onset phase from reported sleep times, and showed wake time and midpoint of sleep to be better predictors than bedtime. Indeed, the wake time regression equation is remarkably similar to that of Burgess and Eastman (Sleep, 2003 Abstract Supplement). In contrast, our ability to predict melatonin onset phase in the school-year group was poorer. More work is required to determine whether multiple regression models that may also include such variables as age and maturational stage, can achieve greater accuracy for predicting circadian phase.

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Circadian Timing and Sleep-Wake Pattern in Swedish High School Students

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Introduction: Teenagers experience often difficulty in falling asleep at reasonable time at night. This study aimed to investigate the sleep-wake patterns in a group of high-school adolescents and to observe any circadian phase change.

Methods: Twenty students (10 females and 10 males, 17-19 years old) in the last year of the Swedish upper secondary school were enrolled. They were healthy, without sleep problems. All attended the same school in Gothenburg; 19 completed the study. They filled up a 34-item questionnaire concerning lifestyle, (stress, daytime condition, stimulants, tobacco, medication, entertainment), sleep habits and quality. Epworth Sleepiness Scale (ESS) and Karolinska Sleepiness Scale (KSS) were used to estimate sleepiness Sleep/wake was assessed using actigraphy and sleep diary for 2 weeks.

Results: All subjects presented irregular sleep-wake schedule with eveningness pattern - late bedtime and wake-up time. They reported significantly less time in bed on school nights (they woke earlier), compared to weekend nights. Caffeinated beverages did not influence night sleep. One third reported bad sleep quality or/and difficulty in falling

asleep. Sleepiness scales did not show advanced daytime sleepiness (mean value of ESS 6.4 (SD 2.8) - only one subject had a value of 12 - KSS mean value 6 (SD 2). Actigraphic data confirmed irregularity of the sleep-wake pattern. More nocturnal awakenings were observed in actigraphy than reported in the sleep diary. The periodograms consisted of flat curves, lacking major peak, as compared to the clear peak at 24 hours observed in normal adults. Time at which subjects went to bed varied greatly from night to night, with variations in time to bed of > 5 hours for 11 subjects, between 3 and 4 hours for 6 subjects and < 2 hours for 2 teenagers only. Often a saw-tooth pattern could be observed during the week, with a progressive delay in bedtime and reduction of sleep during schooldays with recovery during the weekends specially Saturday, when some of the students were able to sleep for more than 15 hours. Two further adolescents presenting the same pattern had their rectal temperature monitored continuously during 3 days. Nadir of the temperature was between 8 and 9 in the morning, and acrofas around 9 at night.
Conclusion: Circadian rhythms were severely disturbed in this homogenous group of high-school students with phase delay, irregular sleep pattern and cumulative sleep deprivation during school days, compensated for during free-time. There were no obvious daytime consequences such as impairment of academic performance or increased daytime sleepiness. Circadian changes are related not only to sleep patterns but also to impact of modern lifestyle. Teenagers remain active at night with late entertainments (TV, internet) and an urge to communicate (cell phones). Although educational programs informing youngsters about the risks of poor sleep habits can yield some results, they seldom manage to convince them to change their lifestyle. To avoid the building up of sleep deprivation, changes in school schemes are necessary and sleep schedules have to be adjusted, considering even unusual approaches - such as promoting polyphasic sleep.

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Melatonin-Induced Phase Delays of the Human Circadian Pacemaker

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Introduction: In most totally blind individuals, the lack of photic input to the human circadian pacemaker results in free-running circadian rhythms that drift progressively later (rarely earlier) in accordance with a period typically > 24 h. Such blind free-runners (BFRs) suffer from recurrent nighttime insomnia and daytime somnolence and have objective decrements in sleep quality as documented by polysomnography. Administration of exogenous melatonin has been shown to entrain BFRs according to a phase response curve (PRC) to melatonin resulting in improvement in sleep quality. Despite the fact that several PRCs to melatonin have demonstrated both phase advances and phase delays, the phase-delaying effects of melatonin have been questioned by some investigators. We show here clear phase delays induced in BFRs by oral melatonin.
Methods: Two healthy bilaterally enucleated individuals, BL-35 (51 y.o. F) and BL-30 (57 y.o. M), were admitted to the Oregon Health & Science University General Clinical Research Center at approximately 2-week intervals for 24 hours for hourly sampling of blood to assess the plasma melatonin onset (MO) with a 10 pg/ml threshold [defined as circadian time (CT) 14] or a 2 pg/ml threshold (CT 13). Plasma melatonin concentrations were measured by radioimmunoassay with an antibody raised in the laboratory of Kennaway and co-workers and reagents supplied by American Laboratory Products (Windham, N.H.). Circadian period (tau) was calculated by linear regression through a series of MOs and interpolation between two successive MOs (2-point tau). Following assessment of baseline free-running tau, melatonin was administered (0.5 mg in BL-35 and 0.05 mg in BL-30) at a circadian phase predicted to induce phase delays (i.e., CT 18-6). A third subject, BL-29 (47 y.o. F), had maintained entrainment to 0.05 mg for one year and then began to free-run: her dose was increased to 0.075 mg on the delay zone of the melatonin PRC.
Results: Pre-treatment linear regression taus were 24.0015±0.0004 h, 24.23±0.04 h and 24.37±0.05 h for BL-35, BL-29 and BL-30, respectively. The longest 2-point taus without melatonin were 24.07 h, 24.35 h and 24.54 h, respectively. Melatonin administered on the phase-delay zone of the melatonin PRC induced robust increases in observed circadian period in all three subjects: daily delays were 0.28 h to 0.46 h greater than the longest pre-treatment two-point tau (the longest 2-point taus with melatonin were 24.53 h, 24.63 h and 24.85 h, respectively). In all three instances, phase delays were observed when melatonin administration occurred on the delay portion of the melatonin PRC. Initial CTs of administration for BL-35, BL-29, and BL-30 were 1.5, 0.9, and 5.6 respectively. The longest 2-point taus occurred when melatonin was initially administered on the delay zone.
Conclusion: Melatonin is capable of inducing significant phase delays in the timing of the human circadian pacemaker. These data have implications for resetting circadian phase using exogenous melatonin in sighted individuals with Advanced Sleep Phase Syndrome (ASPS), blind individuals entrained at an abnormally advanced circadian phase and in BFRs with taus < 24 h. Melatonin is capable of maintaining entrainment to a forcing period significantly greater than 24 h, such as the Martian day (24.66 h). Lower doses of melatonin have less spillover and therefore are capable of being more selective in stimulating the advance or the delay zone of the melatonin PRC. Doses as low as 0.02 mg have been found capable of entraining BFRs.

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Is The Phase Advance Of Circadian Rhythms In The Middle Years Of Life Related To Habitual Patterns Of Light Exposure?

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Introduction: We reported that compared to young subjects, middle-aged subjects exhibit both earlier sleep timing and a phase advance of their circadian temperature rhythm. The mechanisms that underlie the phase advance of the biological clock in aging have yet to be determined. Habitual light exposure pattern may be a determinant factor of earlier phase entrainment in aging. The aim of this study was first, to corroborate a phase advance of circadian rhythms in middle-aged subjects using melatonin as a circadian marker. Second, we sought to determine if the circadian phase difference between young and middle-aged subjects is related to different patterns of habitual light exposure.
Methods: Thirty-one healthy subjects between the ages of 20 and 60 were studied (16 women, 15 men; mean age 42.3 y. sem=12.0). Habitual light exposure was measured in 1 minute samples by an ambulatory wrist monitor for 7 days prior to laboratory studies. Participants were submitted to a mini-constant routine for 25 hours. During this time subjects remained awake in a semi-recumbent position in constant environmental conditions in dim light intensity (<10 lux). Saliva samples were collected every 30 minutes and melatonin concentration was determined by radioimmunoassay. Habitual light data for the seven days were log-transformed and averaged over each hour. Melatonin onset was calculat-

ed by interpolation using a threshold of 1.3 pg/ml, which represents twice the least detectable dose (0.65 pg/ml). Correlations were performed to evaluate the relationships between age, melatonin onset and habitual light exposure. T-tests were used to evaluate differences between young (6 women and 7 men; 20-39 y.; mean age 29.6 y. sem=5.4) and middle-aged subjects (10 women and 8 men; 40-60 y.; mean age 51.4 y. sem=4.8).
Results: Melatonin onset was significantly associated with age (r=-0.56, p=0.001). On average, melatonin onset occurred 1.3 hour earlier in middle-aged compared to young subjects (p=0.02). Increasing age was associated with higher levels of habitual light exposure in the morning between 09:00-10:00 (r=0.48, p=0.01) and between 10:00-11:00 (r=0.45 and p=0.02). Age was not associated with habitual light exposure at other times of day. Habitual light exposure between 09:00-10:00 and 10:00-11:00 were not significantly associated with melatonin onset in the entire group or in each age group separately (p>0.05).
Conclusion: These results confirm that a phase advance in the output of the circadian timing system appears during the middle years of life. This phase advance is of the same magnitude as the one reported in healthy elderly subjects. Age was only associated with habitual light exposure between 09:00 and 11:00 and not to other times of the day. Nevertheless, habitual light exposure at this time of day could not explain the phase advance of the melatonin circadian rhythm with increasing age. We conclude that habitual light exposure is not a key factor underlying age-related changes in the phase of the circadian timing system in the middle years of life.

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The Daily Rhythm of Brain Blood Flow

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Introduction: CBFV (cerebral blood flow velocity) is lower in the morning than in the afternoon and evening. Two hypotheses have been proposed to explain the time of day changes in CBFV. First, CBFV changes are an evoked effect secondary to sleep associated processes, and second, time of day change in CBFV is due to an endogenous circadian rhythmicity driving CBFV lower at night independent of sleep. The aim of the study was to examine CBFV over 30 hours of sustained wakefulness to determine whether CBFV exhibits fluctuations associated with time of day.
Methods: Nine subjects underwent a modified constant routine protocol. CBFV from the middle cerebral artery was monitored by chronic recording of Transcranial Doppler (TCD) ultrasonography. Other dependent variables included core body temperature (CBT), end-tidal CO2, blood pressure, and heart rate. Salivary dim light melatonin onset (DLMO) served as a measure of endogenous circadian phase position.
Results: A non-linear multiple regression, cosine fit analysis revealed that both the CBT and CBFV rhythm fit a 24 hour rhythm (R2=.79 and R2=.50, respectively). FFT analysis revealed that all subjects showed a cycle of ~ 24 hours in CBT and in seven out of nine subjects for CBFV. Salivary DLMO occurred 6-10 hours before CBT nadir in seven out of nine subjects, which is consistent with the literature. Comparison of the CBFV nadir to the CBT nadir revealed differences ranging from 1 to 9.5 hours across subjects, yielding a mean difference of 6 hours or 90 degrees. In seven subjects, the CBFV nadir was delayed with respect to the CBT nadir and in two subjects the nadir was advanced. Once the nadirs were aligned, the CBFV rhythm closely tracked the rhythm of CBT (r=.76, p=<.01).
Conclusion: Time of day variations in CBFV appeared to show an approximately 24 hour rhythm under constant conditions, suggesting it may be regulated by a circadian oscillator. The 90 degree delay between the CBT and CBFV rhythm may help explain alertness in the evening before habitual bedtime and may contribute to sleep inertia in the morning after waking up. This delay is consistent with the lower CBFV values found in the morning in previous studies and corresponds to the time period of during which there is an increased incidence of strokes. The mechanisms by which delay is occurring have yet to be explained.

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Cockpit Light Exposure In Flight Crew Spanning 30 Days Of Night Flight Activity

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Introduction: Studies have shown that fatigue in aviation is greater during nighttime operations than during daytime operations and is partially attributable to limited light exposure. Although less than 200 lux, has been shown to be an effective countermeasure in obtaining an alerting response both subjectively and physiologically, there is currently no formal regulation concerning the use of light in commercial aircraft cockpits during night flights. The present field study examined the intensity of light exposure obtained by pilots during nighttime flights over 30-days to examine if any differences existed between captain and first officer positions in both domestic and international operations.
Methods: Sixteen domestic pilots (mean age = 37.63 ± 2.17 years) and 9 international pilots (mean age = 43.33 ± 3.67 years) who possessed an Airline Transport Pilot license and active flight schedules participated in the field study. They (n=24 male; n=1 female) included 13 captains and 12 first officers who wore a light sensor (Actiwatch-L, Mini Mitter Co., Inc., Bend, Oregon) around their neck, approximately 10 cm below the chin to measure light exposure. Each pilot flew multiple flights during the study, but only flight segments that operated between sunset and sunrise were analyzed (M = 8.82 ± 6.87).
Results: A two-factor Analysis of Variance was conducted on light exposure measured in lux (dependent variable), and flight type and position (independent variables). Analyses showed main effects for both flight type, $F(1, 185) = 11.69$, $p = 0.001$ and position, $F(1, 185) = 14.87$, $p < 0.001$, and an interaction between flight type and position, $F(1, 185) = 13.99$, $p < 0.001$. In regards to flight type, the light exposure obtained in the cockpit by domestic pilots (M = 70.43 ± 35.54) was less than international pilots (M = 472.98 ± 112.25). Based on position alone, captains obtained less exposure to light (M = 44.70 ± 81.02) than first officers' exposure to light (M = 498.71 ± 85.43). Much of these differences were due to the light exposure obtained by the international first officers (M = 920.17 ± 163.35).
Conclusion: These results provide an approximation of the amount of light obtained by pilots in the cockpit during nighttime flight operations over a month of flight activity, and demonstrated that flight decks can provide adequate light sources during night flights that may be used to promote alertness. The variability in the amount of light exposure demonstrated that its current use on the flight deck is sporadic. Further analyses will be conducted to examine possible causes of the differences

in light exposure that existed not only between the type of flight operation but also between flight positions. However, before the results can be transitioned to the operational environment, further research is required to demonstrate the operational feasibility of using light in the cockpit as a potential countermeasure to mitigate the soporific effects of nighttime flight operations.

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Alteration In The Interaction Between Circadian And Sleep Homeostatic Processes In Delayed Sleep Phase Syndrome

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Introduction: Delayed Sleep Phase Syndrome (DSPS) is the most common primary circadian rhythm sleep disorder. Individuals with DSPS seek treatment because enforced socially acceptable bed times and wake up times result in insomnia, excessive sleepiness and functional impairments. In order to understand the pathogenesis of DSPS in a clinical population, we performed a detailed comparison of sleep and circadian rhythm parameters between individuals who sought treatment in the sleep clinic with those who were recruited from the general population for research studies.
Methods: This study was approved by the Northwestern University IRB. A total of 28 subjects (mean age 32; range 19-59 years) who met ICSD criteria for DSPS and 40 normal control subjects participated in this study. Of these, 12 subjects sought treatment for their condition (physician-referred group) and 16 subjects responded to advertisements for a research study (self-referred group). Sleep/wake activity was measured using wrist actigraphy and sleep diaries for a period of at least 7 consecutive days. Sleep onset, sleep offset, total sleep time (TST), and sleep efficiency were calculated using the Actiwatch software. Salivary melatonin samples were collected every 30 minutes beginning 4 hours prior to habitual bedtime until sleep time under dim light conditions (<50 lux) to determine dim light melatonin onset (DLMO). Core body temperature was recorded for 48 hours to determine the temperature minimum (Tmin). All sleep/wake parameters were calculated for the entire week, weekdays and weekends.
Results: When compared to controls, sleep and circadian phases were delayed for the entire DSPS group (physician and self-referred) for sleep onset, sleep offset, DLMO and Tmin ($p \leq .001$). Although sleep onset, sleep offset and TST were similar between the two groups of DSPS subjects for the entire week, the physician-referred group showed an earlier DLMO when compared to the self-referred group (22:38 ± 0:51 vs. 24:00 ± 1:21, $p=.03$). In addition, the interval from DLMO to sleep onset and DLMO to sleep offset was longer in the physician-referred group ($p \leq .05$). These findings were more evident during the weekend. In addition to the prolonged interval between DLMO and sleep onset and sleep offset, the physician-referred group woke up approximately one hour later ($p=.06$) and slept approximately one hour more than the self-referred group ($p=.02$) on the weekend. Differences between physician-referred and self-referred subjects in TST on the weekends suggest that the physician-referred group accrue a greater sleep debt on weekdays than the self-referred population.
Conclusion: The results of this study indicate that both alterations in circadian phase and sleep homeostatic regulation play important roles in the pathophysiology of DSPS in the clinical population. Furthermore, decreased ability to recover sleep and/or phase intolerance may contribute to the severity of symptoms in these individuals. A better understanding of the pathophysiology of DSPS will lead to improved therapeutic approaches.

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An Endogenous Circadian Rhythm In Bronchodilator Rescue Medication Use in Asthma

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Introduction: In many patients with asthma, pulmonary function worsens and asthma symptoms increase at night, producing the condition known as nocturnal asthma. The relative influence of sleep per se and of circadian rhythms (independent of sleep) on the expression of nocturnal asthma has not been addressed using validated circadian techniques. Our aim was to test whether or not there exists an endogenous circadian rhythm in symptom based rescue medication use in asthma by using a forced desynchrony protocol.
Methods: We studied 15 adult subjects with asthma during a forced desynchrony protocol such that all behaviors (including the sleep/wake cycle) occurred evenly across all phases of the circadian cycle. This was achieved by scheduling a recurring artificial day length of 28 hours while subjects lived in dim light in a 'time isolation' laboratory. Subjects were instructed to take their bronchodilator rescue medication (beta2-adrenergic agonist inhaler) based on their perceived need due to symptoms alone. Data from the last 6 consecutive 28 hour 'sleep/wake' cycles were analyzed. Times of inhaler use were assigned a circadian phase (0 degrees = minimum core body temperature) and grouped into bins of 60 circadian degrees (approx. 4 hours). The proportion of each subject's total inhaler use was calculated for each circadian phase bin to ensure that each subject contributed equally to the group distribution. To assess circadian rhythmicity, the proportions in different circadian phases were compared.
Results: Only 9 of 15 subjects used their rescue medication during the study. In those 9 subjects, medication was used on a total of 54 occasions (median 5; range 1 to 14 among subjects). Of the 54 occasions, 73% occurred in the 3 consecutive circadian bins centered around the usual sleep period (bins 300, 0 and 60 degrees). This was significantly higher than the 50% of occurrences that would be expected by chance in these 3 bins ($p=0.038$). Thus, only 27% of rescue medication doses occurred in the 3 consecutive circadian bins that correspond to the usual afternoon and early evening. This trend across circadian cycle was much more pronounced in the 3 subjects with defined nocturnal worsening of asthma (i.e., those demonstrating a consistent overnight drop >12% in forced expired volume within 1 second [FEV1] during the screening process). However, there was no endogenous circadian rhythm in FEV1 immediately preceding medication use in these subjects. The proportion of medication uses occurring from sleep was 48% (26 of 54), which was higher than expected (as 33% of the protocol was assigned as sleep opportunity).
Conclusion: In subjects with asthma there exists an endogenous circadian rhythm in symptom based rescue medication use with more medication taken around the circadian times when sleep normally occurs. There was also a trend for increased medication during scheduled sleep opportunities (independent of circadian phase). This rhythm is particularly striking in subjects with nocturnal worsening of asthma based on pulmonary function. This circadian rhythm in medication use could result from endogenous rhythms in baseline pulmonary function, in the ventilatory requirements and/or in the sensations of respiratory discom-

fort.

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Sleep Length, Phase Shifts, and Age Affect Reliability of Morningness-Eveningness Scales

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Introduction: Recent morningness/eveningness (M/E) scale-score distributions of university students show unusual eveningness score increases with reduced morningness scores. One possibility is that sleep alterations encourage eveningness-like responses to scale items despite the underlying circadian disposition. This would shift M/E distributions of the MEQ scale (Horne-Ostberg) and BALM scale (Brown) more toward eveningness and could misclassify individuals. Sleep length, phase advance, and age were evaluated for influence on M-E scale stability and distribution.
Methods: Both MEQ and BALM scales were completed by 1,370 university students (age: mean=18.74; SD=1.53; male=40.9%, female=57.1%, unknown=2.0%); plus additional open-ended questions about typical weekday (versus preferred) bedtimes and awakening times, and average weekday sleep duration. Sleep-length groups were: short (SS, n=512) 6.5 hrs, medium (MS, n=420) 6.6-7.4 hrs, long (LS, n=438) 7.5+ hrs, Phase-shift groups were calculated from preferred minus actual awakening times: low (LoP) <1.0 hour, moderate (MdP) 1.0-1.99 hours, high (HiP) 2+ hours. Age groups were: 18yrs, 19yrs, 20+yrs. Internal consistency (IC) measures for BALM and MEQ samples were made using Cronbachs alpha. Shifts in M-E scale distributions were evaluated using Kolmogorov-Smirnov (K-S) two-sample tests as paired comparisons.
Results: MEQ and BALM scales correlated significantly (Pearson r=.874) with overall Cronbach-alpha reliability values of .79 and .78, respectively. IC showed systematic reduction with increasing phase (LoP-MdP-HiP) advance [MEQ: LoP=.81, MdP and HiP=.76; BALM: LoP=.82, MdP and HiP=.74] more prominently than from reduced (LS-MS-SS) sleep length [MEQ: LS=.80, MS=.78, SS=.77; BALM: LS=.78, MS and SS=.77]. In combination, increased phase advance (LoP-MdP-HiP) and reduced sleep length (LS-MS-SS) resulted in a decline of IC alpha values in a dose-response manner. For MEQ: (LoP/LS=.82, LoP/MS=.80, LoP/SS=.79, MdP/LS=.77, MdP/MS=.76, MdP/SS=.74, HiP/LS=.77, HiP/MS=.77, HiP/SS=.74). For BALM: (LoP/LS=.82, LoP/MS=.82, LoP/SS=.81, MdP/LS=.77, MdP/MS=.73, MdP/SS=.72, HiP/LS=.76, HiP/MS=.70, HiP/SS=.74,). Furthermore, age effects on IC of these two were most apparent in the 18/19-yr-old groups; phase for MEQ: (LoP=.82/.77, MdP=.75/.78, HiP=.74/.75); phase for BALM: (LoP=.82/.79, MdP=.71/.75, HiP=.72/.75. Sleep for MEQ (LS=.79/79, MS=.79/.75, SS=.75/.76); sleep for BALM: (LS=.78/78, MS=.76/.79, SS=.75/.74). Rather stable IC values were obtained for 20+- yr-olds regardless of sleep alterations. Phase for MEQ: (LP=.83, MP=.77, HP=.87); phase for BALM: (LP=.85, MP=.79, HP=.84). Sleep for MEQ: (LS=.87, MS=.80, SS=.81); sleep for BALM: (LS=.84, MS=.80, SS=.83). Regardless of sleep length, 2+ hours of phase advance shifted both MEQ and BALM distributions towards more eveningness (K-S: $p<.05$). For MEQ only, the SS group shifted toward eveningness when phase advanced 1+ hours (K-S: $p<.05$) indicating greater susceptibility toward distortion for the MEQ than for the BALM scale.
Conclusion: Many college students indicate shorter- and more phase-shifted sleeping patterns than preferred, which may influence their item responses on M-E questionnaires in a dose-response manner. Reduced sleep length combined with increased phase shifting result in greater estimates of eveningness and reduced estimates of morningness that may not correctly reflect underlying circadian timing. These results suggest that whenever a M-E questionnaire is used, the Cronbach-alpha reliability value should be evaluated as an important indicator of the strength of its ability to correctly assess M-E sample distributions and to correctly identify chronotype status.

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Sleep Behavior and Eye Closure States in Mature Greater Rheas (Rhea americana)

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Introduction: Sleep is a necessary component of life. Sleeping at optimal times and in optimal postures could mean the difference between life and death. Some animals have found a way to protect themselves by being in a state of sleep and wakefulness at the same time where one cerebral hemisphere stays alert while the other sleeps. This is known as unihemispheric slow-wave sleep (USWS), in birds this is shown by unilateral eye closure (UEC). In this study, we observed the sleep-wake behavior, head orientation, and UEC in Greater Rheas (Rhea americana), large flightless birds. Rheas represent an ancient line of birds which could provide insights into the functions of sleep.
Methods: The study was conducted on three rheas, purchased as 4-week old juveniles from a local farm and raised in our sleep laboratory animal facilities. We developed a rhea husbandry protocol of 12/12 LD (lights on 6:00, off 18:00h) simulated sunlight (100 lux) and moonlight (0.5 lux). Water was provided ad-libitum. Feeding was once per day with commercial ratite food and custom probiotic supplements. The rhea room (4 X 6 m) was maintained between 74-78 F, and contained duck decoys and rubber matting to enhance the environment. The room had one door from which the caretaker entered. Behavior was videotaped 24h/day, for 20 weeks using eight digitally switched cameras strategically located around the room. Recording was at 60 frames/s yielding a 0.13-s resolution /frame. Eye closure states (unilateral and bilateral) and behaviors were recorded instantaneously every min.
Results: Rheas preferred to sleep in corners or near duck decoys. Younger birds would often sleep next to or leaning on a conspecific bird. During the night the rheas spent 59.7% (n=2038) of their time with their head up, 37.6% (n=1283) with their head curled back, and 2.7% (n=91) with their head on the ground. Head and eye orientation was maintained towards the main entry-way (>94%) at night and in UEC. During night sleeping, the range of sleep was from 2.4 to 6.3 hrs (average=4.1 +/- 1.4 hrs). On average the focal rhea spent approximately 60% of its time awake and 40% of its time asleep in a 12hr night. UEC durations averaged 18.3 +/-10.1s and ranged between 2-54s in duration.
Conclusion: This study follows preliminarily observations by Amlaner et.al., (Sleep 24:202, 2001) who characterized the basic sleep behavior and eye-states of rhea chicks. Our current analysis spanning 5 months of continuous 24hr video data indicates that average sleep duration for rheas is similar to most modern bird species that our laboratory has previously reported. However, our earlier report on rhea chicks under emphasized the role of two sleep postures as the animals matured; head up and head curled back on the neck. These postures were observed more frequently as the birds matured and they are more vigilant sleep postures that allow greater potential for maturing birds to detect predators. The head on ground posture, commonly adopted by chicks, does not provide as clear a visual pathway. Our observations of head and eye orientation suggest that rheas do maintain vigilance during sleep, particularly toward entry-ways to the room, which are possibly seen as a potential source of disturbance or threat.

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Electrophysiological Correlates of Migratory Sleeplessness in the White-crowned Sparrow (Zonotrichia leucophrys gambelii)

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Introduction: During the spring and fall, migratory songbirds such as the White-crowned Sparrow fly thousands of kilometers to reach their breeding and wintering grounds, respectively. Despite sleeping at night during the non-migratory seasons, songbirds fly at night during migration and remain active throughout much of the day. Whether such birds sleep in flight, engage in daytime sleep or curtail sleeping altogether during migration is unknown. We herein report the first electrophysiological recordings of migratory songbirds that indicate a capacity to markedly reduce time spent sleeping during migration.
Methods: We instrumented 8 adult (one-year-old) sparrows for EEG and EMG recording in July 2003. EEG electrodes were placed over the left and right cerebral hemispheres and referenced to an electrode over the cerebellum. Behavior was recorded via infrared activity monitoring and video recording. Each bird was continuously recorded for up to four months under a 12:12 LD schedule. Representative 24-hour periods were scored prior to and during migration. Behavioral state was categorized as wakefulness, drowsiness, SWS and REM sleep.
Results: All birds showed nocturnal migratory behavior starting in July-August that included hopping back and forth and flapping their wings. During such migratory restlessness, the birds kept both eyes open and EEG activity in both hemispheres showed an activated pattern indicative of wakefulness. In both non-migrating and migrating birds, SWS and REM sleep were restricted to the dark phase of the LD cycle, with sleep usually occurring during the first third of the night in migrating birds. In five birds that were recorded prior to and during migration, sleep was reduced during migration (non-migrating vs. migrating: mean % recording time ± SD): wakefulness (48.2±3.6% vs. 62.7±2.8%; $p<0.001$); drowsiness (17.9±2.2% vs. 24.5±2.7%; $p<0.001$); SWS (28.3±3.3% vs. 11.0±3.4%; $p<0.001$); and REM sleep (5.5±1.3% vs. 1.8±1.0%; $p<0.001$). When compared to non-migrating nights, REM sleep latency from SWS onset was 11.7±8.0 minutes shorter on migrating nights ($p=0.03$) and REM sleep encompassed a larger proportion of time during the first half of migrating nights. Migrating birds spent 45.4±36.7 more minutes in drowsiness during the day when compared to non-migrating birds ($p<0.01$). The three remaining birds that were migrating throughout the experiment showed sleep patterns indistinguishable from those observed in the other five birds during migration.
Conclusion: These data demonstrate that migratory songbirds markedly reduce sleep during migration. Interestingly, during migration REM sleep was more prevalent during the first half of the night. This may reflect a circadian shift in REM propensity related to migration and/or a homeostatic response to prior REM sleep restriction. Although there was an increase in time spent in drowsy behavior during the day in migration, sleep loss at night was not compensated for by an increase in sleep during the day. The spontaneous changes in sleep during migration may provide a powerful model in which to study sleep homeostasis, the effects of sleep restriction on performance and memory consolidation, as well as changes in sleep architecture in mood disorders which are similar to those observed during migration.

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Characterization of a Sleep-like State In Adult Zebrafish

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Introduction: Zebrafish are commonly used in developmental genetics and have a large potential for the study of the genetics of behavior. Technically, transgenic animals and mutagenesis screens are easy to conduct in this specie, allowing the discovery and the study of genes related to behavior. Like mammals, zebrafish are verteberates, and have the classical monoaminergic and hypocretinergic cell groups. They also have a relatively large genome (~1700 Mb) when compared to Drosophila (~180 Mb), making it more similar to humans (~3200 Mb). Sleep-related genes have been characterized in Drosophila and mammals, but not in zebrafish. This study aimed at characterizing sleep like behaviors in zebrafish, using classical behavioral criteria.
Methods: Adult fish (3 months to 2 years old, n=30) behavior was monitored using an automatic infrared video recording system. Fish were housed individually in recording chambers [>40 mL for young adults (less than 3 month), 200 mL for adults]. Recordings were done in either light:dark conditions (14:10 L:D) or in constant darkness (DD). Video images (frame rate = 30 images/second) were acquired and analyzed on a PC using a software developped in house. This software was a modification of the previously published FishWatch software, courtesy of Steve Wang and Dr. Zhdanova. Position, direction, and clock time were determined for each image and relative movement determined. For further characterization, arousal thresholds (minimum stimuli inducing a movement) were measured after pulse application of electric current while the fish was in an immobile, sleep-like state. Studies aiming at repetitively interrupting the sleep-like state were also performed,
Results: Video recording showed the occurrence of a clear, prolonged state of immobility in all zebrafish animals. This state can be quickly reversed after stimulation. A characteristic posture (tailfin pointed downward) and preferred tank position (either at the surface or the bottom of the recording chamber) was consistently observed during sleep-like immobility periods. Rhythmic locomotor activity was evident in both LD and DD conditions, with the immobile periods typically occurring during the biological night. Electrical stimulation was able to immediately reverse the sleep-like state into an active state. Preliminary results after repetitive stimulation interrupting immobility during the night resulted in rebound immobility upon cessation of the stimulation.
Conclusion: The stereotypic nature of the immobile posture, its reversibility after stimulation and likely homestatic and circadian regulation are suggestive of a sleep-like state similar to mammalian or drosophila sleep. We are now completing the characterization of this state and developing a high throughput automatic recording systen using our own software and monitoring apparatus. We anticipate using this system to evaluate transgenic and randomly mutagenized animals.

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Association Between EEG Asymmetry And Eye State In Bottlenose Dolphins And Northern Fur Seals

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Introduction: Previously we reported about an association between EEG asymmetry (or unihemispheric slow wave sleep-USWS) and eye state in one Cetacean species - beluga or white whale (Lyamin et al., 2002). Visual observations provide growing evidence that other Cetaceans and Pinnipeds show unilateral eye opening/ closure / blinking. This suggests that a relationship between EEG asymmetry and asymmetrical eye state is characteristics of many aquatic mammals.
Methods: We examined an association between the interhemispheric EEG asymmetry and eye state in two adult bottlenose dolphins (Tursiops truncatus) and two northern fur seals (Callorhinus ursinus). In dolphins EEG was recorded from intracranial electrodes implanted over symmetrical areas of the two hemispheres during one and three days. During recording the dolphins were placed in a 4x4x1.2 m pool with seawater. In fur seals EEG, EMG and EOG were recorded in a 1.5 x 1.5 m indoor enclosure and they slept only on land. The duration of recording in seals lasted 3 days. Eye state was sampled (when visible) during recording and scored in 20 sec (seals) and 30 sec (dolphins) epochs as open, closed, or intermediate. EEG spectral power was computed in the range of 1.2-4.0 Hz for two symmetrical recordings. The EEG stage of each hemisphere was also scored visually as desynchronization, low amplitude and high amplitude synchronization.
Results: The asymmetry in eye state in the dolphins and seals studied here correlated well with the pattern of EEG activity in two hemispheres as described in the beluga (Lyamin et al., 2002). For instance, in dolphin 1 during the first 2 recording days, the eye contralateral to the more deeply sleeping hemisphere remained closed 60% and 55% of the USWS time and each eye was in an intermediate state 35% and 37% of this time (respectively, for right and left eyes). At the same time, the eye contralateral to the waking hemisphere was in an intermediate state or open (95 and 98% of the time). In both seals, each eye was closed in the great majority of all epochs with higher amplitude EEG in the contralateral hemisphere compared with the ipsilateral hemisphere (97% and 80%, respectively for right and left eyes) as judged by both EEG spectral analysis and visual scoring. One eye was occasionally blinking (1-2 blinks per 20 sec) about 60% of the time when the contralateral hemisphere was less synchronized (more activated) than the ipsilateral hemisphere. Bilateral eye closure was rare in dolphins (2% of the recording time) and not necessarily associated with high amplitude unihemispheric and asymmetrical SWS (only 33% of bilateral closure time). On the contrary, the fur seals slept mainly with two eyes tightly closed (up to 90% of the time when the two eyes were visible). No noticeable interhemispheric EEG asymmetry was recorded when the two eyes were closed.
Conclusion: The present data convincingly supports the idea that one of the functions of USWS/interhemispheric EEG asymmetry during sleep in Cetaceans and Pinnipeds is visual monitoring the environment serving in the avoidance of predators and maintaining sensory contact with others animals.

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Changes in Cognitive Functions, Sleep, and Breathing Characteristics Following Adenotonsillectomy in At-Risk Preschool Children with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is associated with reduced daytime functioning in both adults and children. Socio-economically challenged pediatric populations may be particularly vulnerable to these effects since animal models have shown that environmental impoverishment may enhance the effects of OSA. Studies on the beneficial impact of treatment for OSA in children support the need for early intervention, but have been restricted to small, clinical populations encompassing a wide age range. This study examined the impact of adenotonsillectomy (T&A) in young children with OSA in a highly vulnerable, at-risk community population.
Methods: A validated questionnaire was distributed to parents of financially at-risk preschoolers attending state-sponsored education programs. Those whose survey indicated presence of snoring >3 days/week underwent standard overnight polysomnography (PSG) and cognitive testing using the Differential Ability Scales (DAS). Nineteen subjects were diagnosed with OSA, underwent T&A, and returned for follow-up PSG and cognitive testing 4.0 (SD+0.96) months later. Control children without snoring were matched for age, gender, ethnicity, and maternal education, and underwent overnight PSG and cognitive assessment.
Results: Prior to T&A, DAS scores were significantly lower in OSA (x = 82.5 [SE = 3.2]) versus controls (x = 94.0 [SE = 5.7]; p=0.01); following T&A, OSA DAS scores (x = 87.2 [SE = 3.4]) improved compared to pre-operative scores (p=0.02) and did not differ from matched controls. Following T&A, delta sleep percent increased (p=0.01) and REM sleep percent decreased (p=0.003) in OSA; compared to controls, pre-operative awake percent was greater (p=0.03), and delta sleep percent was reduced (p=0.01). Following T&A, respiratory arousal index (p=0.02), total arousal index (p=0.01), apnea-hypopnea index (p=0.006), and apnea index (p=0.02) were all improved. There were no significant differences between OSA post-operative sleep or respiratory measures compared to controls.
Conclusion: Following surgical treatment, at-risk preschool subjects diagnosed with OSA improved their cognitive scores, and normalized their sleep and breathing patterns. The current sample was recruited directly from the community and represents a unique and particularly vulnerable population that may not ordinarily seek evaluation and treatment. The current study underscores the potential value of outreach screening programs for sleep-disordered breathing, and particularly for preschool-age low-income groups.

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Contributions of Child Sleep Characteristics, Biomedical Risks, Activities in the Home, and Maternal Learning History to the Development of Phonological Sensitivity and Lexical Retrieval in Preschool Children

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Introduction: Phonological sensitivity and lexical retrieval skills in the preschool period are linked to word-level reading skills at school age. Despite participation in preschool programs emphasizing literacy and phonological skills, childrens skill development is also influenced by background characteristics. Sleep quality and quantity may also impact on childrens cognitive skills and relate to both biomedical and caretaking factors. The contributions of sleep measures, biomedical conditions, child-centered family activities in the home, and maternal learning and reading history to cognitive skills in phonological sensitivity and lexical retrieval of preschool children.
Methods: Participants were seventy-four three-and four-year-old economically disadvantaged children attending a federally funded preschool program, and their families. Parents filled out previously validated questionnaires regarding their childs sleep hygiene and symptoms of sleep disordered breathing, biomedical risk factors (pregnancy and birth complications, as well as child health status), the Home Observation for Measurement of the Environment (HOME) Inventory, and Maternal Learning History (e.g., presence of reading problems at school age, personal reading activities). Children participated in phonological sensitivity (Rhyme Detection and Phonological Processing) and lexical retrieval (Verbal Fluency and Rapid Naming) skills assessments through the research program established at their school.
Results: Lower scores on the child sleep habits questions was associated with poorer scores on Lexical Retrieval Composite (Rapid Automatized Naming, $p<.05$; Verbal Fluency, $p<.01$). Biomedical risks correlated with and predicted phonological sensitivity (Rhyme Detection ($p<.05$) and Phonological Processing ($p<.01$)) and lexical retrieval (Verbal Fluency ($p<.05$) but not Rapid Naming). HOME scores were correlated but not predictive of lexical retrieval scores ($p<.01$). Maternal learning history was predictive of childrens lexical retrieval scores ($p<.05$).
Conclusion: Children with poorer sleep habits scored lower on the measures requiring speed or sustained attention (lexical retrieval), possibility reflecting underlying fatigue consistent with previous studies of school-age children which have linked poor sleep habits and poorer performance on neurocognitive assessments and less focal brain responses with longer latencies during problem solving tasks.

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The Relative Efficacy of Two Brief Treatments For Sleep Problems in Young Mentally Retarded Children. A Randomised Controlled Trial

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Introduction: Settling and night waking problems are particularly prevalent, persistent and are generally considered to be difficult to treat in children with mental retardation, but the numbers of children and families who could benefit from more and better sleep is greater than can possibly receive the attention they need at present by those with adequate training to help them. Intervention trials in this area of sleep research are limited in number. This study aimed to assess the relative efficacy of (a) face-to-face and (b) (as a more feasible approach) booklet-delivered brief behavioural treatment of sleep problems in such children
Methods: The study design was a randomised controlled trial with a wait-list control group. Participants were community-based and were recruited from special nursery schools. These were the parents of 66 severely mentally retarded children aged 2-8 years with settling and/or night waking problems. The interventions were similar both being behavioural. However the parents received them either conventionally face-to-face or by means of a 14 page easy-to-read illustrated booklet. The primary outcome measure was a composite sleep disturbance score derived from sleep diaries kept by parents.
Results: Both forms of treatment were almost equally effective compared with controls. The majority of children who were taking over 30 minutes to settle (5 or more times per week) and waking at night for over 30 minutes (4 or more times per week) improved on average to having such settling or night waking problems for only a few minutes or only 1 or 2 times per week ($H=34.174$ $df=2$ $p<.001$).
Conclusion: Booklet delivered behavioural treatments for sleep problems were effective for 2/3 of children in this population.

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The Influence Of Swaddling On Sleep Characteristics And Arousability In Healthy Infants

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Introduction: Swaddling is an old infant care practice. It favors sleep and reduces crying in irritable infants. As excessive crying is a reason not to put babies on their back to sleep, swaddling could be a method to promote supine sleep in an effort to prevent Sudden Infant Death Syndrome. The safety of swaddling must be controlled before being recommended for wider use. The purpose of this study is to evaluate the influence of swaddling on physiological sleep parameters and arousability in infants.
Methods: 34 healthy infants with a median age of 10.5 weeks (range 6 to 15 weeks) were recorded polygraphically during a night. They slept in their usual supine position. They were challenged successively during REM sleep in swaddled and unswaddled conditions, and vice versa. A first group of 20 infants were only challenged with white noise of 90 dB (A). Cardiac changes were assessed within 10 sec of the auditory stimuli. A second group of 14 infants were exposed swaddled and non swaddled to white noises of increasing intensities from 50 to 100 dB (A) to determine arousal thresholds, defined as the auditory stimuli that induced cortical arousals.
Results: Swaddling promoted a better efficiency of sleep ($p=.023$), more NREM sleep ($p=.036$) and less awakenings from sleep ($p=.007$). In the swaddled condition, following central apnea there were lower minimum of heart rate ($p=.046$) and greater oxygen desaturation ($p=.041$). No differences were found in the frequency or duration of obstructive and central sleep apneas in both conditions. Compared to the free condition, swaddling was associated with a greater increase in heart rate ($p=.018$) following 90 dB (A) auditory stimulation. When sleeping swaddled, polygraphic cortical arousals occurred for significantly lower auditory stimuli that in the free condition ($p=.007$).
Conclusion: Swaddling promotes a better sleep with less awakenings. Motor restraints induced by swaddling could reduce proprioceptive stimulations to the reticular activating system and favor sleep. Swaddling induces increased cardiac responses and arousability following auditory stimulations in REM sleep. In animals, movement restrictions have been associated to increases in parasympathetic activity, associated with greater changes in cardiovascular responses. As already reported, there is a dose-relation between percentage of changes in heart rates and arousal intensity from sleep. Further studies have to be done before this practice can be recommended for infants.

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Is Chronological or Maturational Age a Better Correlate of Sleep in Depressed and Healthy Children and Adolescents?

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Introduction: Several studies have suggested that age-related changes in sleep architecture may differ between depressed and healthy children and may also be gender-dependent. Other studies have suggested that gender differences in sleep in children are minimal and are due to the failure to control for developmental or maturational differences. The present study evaluated the influence of chronological age and developmental age (Tanner scores) on sleep architecture in 57 symptomatic boys and girls with depression who were unmedicated, and in 67 healthy control children, 8-18 years of age.
Methods: All participants underwent a full psychiatric evaluation. Tanner development scores were self-assessed for upper and lower body maturation by comparison to standard pictures. The average of upper and lower body development was computed for each subject. Participants maintained a regularized sleep wake schedule for 5 days followed by two consecutive nights in the lab. Visual stage scoring was conducted on sleep records. Night 1 served as a lab adaptation and all analyses were based on the second night in study. Correlations were computed between sleep measures and Tanner score and with age, separately by gender and group. ANOVAs evaluated age by group by gender interactions using cutpoints of 3 for Tanner scores and 13 for age.
Results: Overall the correlations were higher for chronological age than for Tanner scores, but differed dramatically by group and gender. For girls with depression, age accounted for significant variance (16-26 %) in % REM, time in bed and number of awakenings, compared to 1-17 % for Tanner score. Among healthy girls, age accounted for 10-40 % of the variance in sleep measures with highest correlations for slow-wave (SW) and Stage 2 sleep and REM latency, in contrast to 1-25 % for Tanner score. Age accounted for 23-34% of the variance in % Stage 1, SW sleep and REM latency, with Tanner accounting for 17-23% variance. By sharp contrast in MDD boys, Tanner score accounted for more variance in sleep measures than age, and correlations were higher than in any other group, accounting for 14-50 % of the variance. Moreover, significant age by group by gender interactions were evident for SW, Stage 1 and Stage 2 sleep and REM latency; effect sizes were larger than

for the interaction between Tanner, group and gender.
Conclusion: Chronological age is a better correlate of sleep than maturational level in healthy boys and girls. Tanner score is a stronger correlate than age only in depressed boys. Girls with depression show only small age-related differences in sleep, but chronological age is a better correlate than Tanner score. Thus, developmental changes in sleep may reflect more then the development of secondary sexual characteristics. These findings also suggest that age-related changes in sleep architecture are gender and disease-dependent.

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Gender and Age Differences in Sleep Macroarchitecture in Healthy and Depressed Children and Adolescents

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Introduction: Sleep macroarchitectural abnormalities have been among the most consistent biological findings in adults with major depressive disorder (MDD). The sleep EEG findings in children and adolescents have, however, been considerably more equivocal. The failure to evaluate age and gender effects has been cited as a potential contributing factor. The primary aim of this study was to evaluate the influence of age and gender on differences in sleep macroarchitecture between healthy and depressed children and adolescents.
Methods: 124 children and adolescents, ages 8-18 years of age, participated in the study. Fifty-seven (28 F, 29 M) symptomatic depressed outpatients were compared to 67 normal controls (38 F, 29 M) matched for age. All of the outpatients met DSM-IV criteria for nonpsychotic depression (single or recurrent) and were unmedicated at the time of study. Participants maintained regularized sleep wake schedules for 5 days prior to spending two nights in the sleep laboratory. Night 1 served as lab adaptation and sleep EEG analyses were based on night 2 data. Visual stage scoring was conducted according to standard criteria. ANOVA evaluated the group by gender by age interactions first, followed by simpler effects as warranted. Least-squares multiple comparisons evaluated differences between individual means.
Results: Although strong age differences were obtained for most sleep measures, significant group by gender by age interactions were also evident. Depressed boys had the largest age-related differences compared to all other groups, whereas differences between children and adolescents were minimal in depressed girls. Adolescent depressed boys had the shortest REM latency, the least amount of SW sleep, and highest % stage 1 sleep. Young depressed boys (<13) had longest REM latency and the least Stage 2 sleep compared to all other groups, with SW sleep amounts equivalent to that of healthy young boys. Among young girls (<13), there was significantly less SW sleep in those with depression, but no other significant group differences were evident in females. Age-related differences in the healthy group were greater among boys than girls. Within age group, however, the gender differences were minimal in the healthy controls. The gender differences within the depressed group were substantially larger. Young depressed girls had significantly less SW than young depressed boys, an effect that was opposite to that observed among the adolescents with depression. Similarly young depressed girls had shorter REM latency than depressed boys in the same age range, with the opposite effect evident in the adolescents.
Conclusion: These findings suggest a differential developmental influence on sleep in early onset depression that is heavily dependent on gender. Gender differences may also be evident in age-related sleep differences in healthy individuals, but are substantially smaller than in those with depression, in agreement with studies in depressed adults.

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Nasometry and Sleep Apnea in Children with Surgically Repaired Cleft Palate

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Introduction: Cleft lip and cleft palate comprise the fourth most common birth defect affecting 1 in 700 newborns in the United States. Velopharyngeal closure is expected in the production of most sounds in the English language. Thus, velopharyngeal dysfunction in patients with cleft lip and palate results in a significant speech disability. Surgical procedures aimed at correcting secondary speech abnormalities and velopharyngeal dysfunction, particularly placement of a pharyngeal flap, can result in snoring and significant sleep apnea. The goal of surgical intervention is to sufficiently narrow the nasopharynx so as to relieve the air escape of velopharyngeal incompetence without creating overt sleep apnea. It is generally accepted that anatomic narrowing and subsequent hyponasality results in sleep apnea. However, our recent clinical experience has identified a group of children who have velopharyngeal dysfunction resulting in hypernasality who have co-existing sleep apnea. Nasometry offers a non-invasive means to accurately quantify the degree of nasalance during normal speech and is the preferred method of testing. Although sleep disordered breathing is well known to occur with increased frequency in children with craniofacial anomalies, the specific incidence in children with cleft palate remains unknown. The purpose of this study is to examine the relationship between nasality and the presence of sleep apnea in children with surgically repaired cleft palate.
Methods: This study is a retrospective chart review in which we analyzed an existing cohort of all children with cleft palate evaluated for obstructive sleep apnea syndrome (OSAS) at the Strong Sleep Disorders Center in Rochester, NY from 9/01 through 10/03. Medical records from the Strong Craniofacial Anomalies Center, were reviewed for surgical interventions, speech therapy evaluations and nasometry values
Results: During the enrollment period, 13 children with cleft palate were referred for possible OSAS due to habitual snoring. Surgical interventions, dates of polysomnography and nasometry were recorded yielding 9 pairs of data in 13 patients which PSG and nasometry were obtained without intervening surgical procedures. Of these nine pairs, 6 had hypernasality and OSAS, 2 had normal or hyponasality and OSAS and 1 had hyponasality and did not have OSAS (Chi-Square =5.444; p=0.02).
Conclusion: Under recognition of sleep disordered breathing is common. Identifying factors placing children at increased risk for obstructive sleep apnea are needed. Recognition that sleep disordered breathing occurs in children with hypernasality can help prevent under-referral. Further studies investigating the impact of sleep apnea on neurobehavioral outcomes in children with clefting are ongoing.

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Sleep Disturbances and Common Illnesses in Preschoolers Attending Daycare: Is There an Association?

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Introduction: Preschool-aged children attending daycare are at high risk for contracting common infectious illnesses such as upper respiratory infections (URIs) and otitis media (OM). Sleep disturbances are also prevalent in this age group. Although the association between adequate sleep and optimal immune system functioning has not been fully examined, preliminary research findings support the link. If optimal sleep is required for immunocompetence, logic follows that suboptimal sleep may lead to immunocompromise and render the host more susceptible to infectious illnesses. Thus, the purpose of this preliminary study was to explore associations between sleep disturbances and incidence of URIs and OM in preschool-aged children attending daycare.

Methods: A convenience sample of parents of two- to five-year-old children attending a university-based daycare center completed the Children's Sleep Habits Questionnaire (CSHQ), a 33-item tool that assesses age-relevant sleep domains. The CSHQ also elicits information regarding the child's usual bedtime, wake time, and the total amount of nocturnal and daytime sleep obtained by the child in a 24-hour period. The parents also completed an Illness Diary, which measures the frequency of URIs and OM episodes.

Results: The sample of children included 8 males and 11 females with a mean age of 38.9 months (± 8.4, range 24-50). The average number of hours spent in daycare per week was 40.9 (± 4.6). Average bedtimes and wake times were 20:45 (military time, range 20:00 - 22:00) and 06:54 (range 06:00 - 08:00), respectively. Total sleep obtained during a 24-hour period ranged from 9 to 13.5 hours with a mean of 11.5 (± 1.3). Due to the exploratory nature of the study, the significance level was set at $\alpha = 0.10$. Forty-two percent of the children averaged less than 12 hours of sleep per 24-hour period, which was significantly less than expected for this age group ($t = 1.732$, $p = 0.10$, one-sample t-test.). Approximately 25% of the children experienced one or more sleep disturbances 2 to 4 times per week. Over 30% of the children experienced daytime sleepiness occurring at least 2 to 4 times per week. There were no episodes of URI in 7 (36.9%) children, one episode in 8 (42.1%) and 2 episodes in 4 (21.1%). Three children (15.8%) had one OM episode each. A higher score on the Daytime Sleepiness subscale was significantly associated with an increased frequency of URIs ($r = 0.352$, $p = 0.07$) and OM episodes ($r = 0.453$, $p = 0.03$) (Spearman's rho, one-tailed test).

Conclusion: These preliminary results suggest that the total amount of sleep obtained by preschoolers attending daycare may be less than normative values. The prevalence of sleep disturbances is similar to values reported in the literature; however, daytime sleepiness may be more common. In addition, increased daytime sleepiness, the manifestation of sleep loss, was significantly associated with increased URI and OM frequency. These findings indicate that further examination of the relationship between sleep patterns, including sleep disturbances, and URIs and OM in preschoolers attending daycare is warranted.

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The Effect Of Maternal Smoking On The Resolution Of Apnea Of Prematurity

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Introduction: Maternal cigarette smoking is an independent risk factor for SIDS. Previous study demonstrated that prenatal exposure to cigarette smoke was associated with an increase in obstructive events in term infants. Our recent study has shown that preterm infants born to smoking mothers also have increased obstructive apnea and decreased respiratory arousals. However, the effect of maternal smoking on the resolution of apnea of prematurity is currently unknown.

Methods: Overnight polysomnographic studies were performed in preterm infants before discharge from the nursery and at follow-up in sleep clinic around 45-50 weeks post-conceptional age. The standard infant montage was performed with simultaneous recording of the following parameters; body position, left and right EOG, 3 channels EEG, chin EMG, EKG, thoracic and abdominal inductance plethysmography, nasal airflow, pulse oximetry, end-tidal pCO2, transcutaneous pO2 and pCO2. Any infants with cardiac, neuromuscular, metabolic and endocrine diseases, and infants with incomplete sleep studies were excluded from the study.

Results: Twenty-four infants met the criteria for entry into the analysis, 15 control [C] and 9 preterms infants born to smoking mothers [S]. There was no significant difference in gestational age (31.1±1.1 wk [S] vs. 29.4±0.7 [C]; P=NS) or post-conceptional age at the initial (36.4±0.7 wk [S] vs. 36.6±0.9 [C]; P=NS) and subsequent sleep studies (50.3±1.0 [S] wk vs. 51.7±1.2 [C]; P=NS). Initial study revealed that preterm infants born to smoking mother had elevated apnea index (28.0±8.9 /hr [S] vs. 18.7±3.8 [C]; $P<0.05$) and decreased overall arousal index (31.8±3.1 /hr [S] vs 47.8±5.2 [C]; $P<0.05$). However, the subsequent study demonstrated that resolution of apnea was noted in both control (18.7±3.8/hr [1st] vs.1.9±0.2 [2nd]; $P<0.05$) and maternal smoking group (28.0±8.9 /hr [1st] vs. 2.9±1.0 [2nd]; $P<0.01$). In addition, no significant difference in the overall arousal index was noted between the two groups at the subsequent study.

Conclusion: It is concluded that preterm infants born to smoking mothers have significant increased apnea and decreased arousal response at the time of discharge from the nursery. However, the resolution of apnea of prematurity is not affected by maternal smoking. It is speculated that alteration in respiratory and arousal patterns in preterm infants born to smoking mothers may be due to the effect of prenatal rather than postnatal exposure to cigarette smoke, leading to vulnerability during early infancy period.

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Excessive Daytime Sleepiness in a Children's Sleep Center

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Introduction: Excessive daytime sleepiness (EDS) is a common complaint among children referred for sleep evaluations. The purpose of this

study was to examine groups of children with Narcolepsy (NAR) and Idiopathic Hypersomnia (IH) in comparison to children with EDS who did not ultimately have a diagnosable sleep disorder (NUL).
Methods: A retrospective chart review was conducted at the Sleep Disorders Center at Children's Hospital, Birmingham, Alabama. Records of children who completed an overnight polysomnography followed by an MSLT the following day were reviewed (N=134). NAR (n= 38, 28%) and IH cases (n=45, 34%) were selected from patients diagnosed from 1994-2002 and the NUL cases (n=51, 38%) were derived from cases evaluated in 1999-2002.
Results: The total sample included both African-American (n=76, 57%) and White (n=58, 43%) children, but included significantly more boys (n=91, 70%, chi-square, p<.001) than girls. The percentage of non-white subjects in the total sample (57%) was significantly higher (p<.001) than the percentage of residents under age 20 in 1999 for the state as a whole (27%) or for the county in which the sleep center is located (38%). However, no difference was noted when comparing by ethnic group or by gender and ethnicity simultaneously across any of the research variables. Analysis of variance testing showed significant differences (p< .05) in PSG sleep parameters between the three groups. NAR children were older (Mean years NAR=13.2, IH=11.5, NUL=10.5) and also had more REM periods overnight (NAR=4.8; IH=3.7; NUL=4.0) than the other two groups. In addition, NAR children had shorter mean sleep onset latency (NAR=9.1; IH=21.8; NUL=14.1 minutes), as well as a greater mean spontaneous arousal index (MSAI) in REM (NAR=10.7; IH=8.1; NUL=6.5). In contrast, the NUL group had significantly lower MSAI (NAR=55.2; IH=51.2; NUL=6.1), and lower MSAI in NREM (NAR=43.6; IH=44.1; NUL=6.0) than the other two groups. The comparison of groups by total sleep time (NAR=475; IH=445; NUL=480 minutes) approached significance (p=.066) but no significant comparisons were found for mean sleep efficiency (NAR=86%; IH=87%; NUL=89%), mean number of awakenings (NAR=19.7; IH=14.3; NUL=15), mean REM latency (NAR=123; IH=134; NUL=160 minutes) or PLM arousals (NAR=5.7; IH=1.9; NUL=2.6).
Conclusion: These findings demonstrate the limited capacity of overnight PSG alone to distinguish between NAR and IH or to establish a diagnosis among other children with EDS. Although, NAR children have more spontaneous arousals and shorter sleep latency, they do not necessarily sleep longer, or have worse sleep efficiency than children with IH or EDS, as might be expected. Although the diagnosis of NAR or IH was determined using sleep parameters from the MSLT, the three groups each demonstrate a somewhat distinct pattern of disturbed overnight sleep. As an unexpected result, this sample also shows an increased prevalence of EDS in African-Americans and in boys. In summary, this study supports both the use of MSLTs in pediatric patients to quantify daytime sleepiness and to document the presence of REM in daytime napping, as well as additional research regarding the prevalence of EDS among African-Americans and boys.

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Sleep Cyclic Alternating Pattern In Normal Preschool-Age Children
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Introduction: During development the disappearance of the trace' alternant and the appearance of K complexes and sleep spindles lead to the individuation of the NREM sleep stages reflecting the maturation of the thalamo-cortical pathways and rostro-caudal pons-thalamus connections. (Louis, 1998). During NREM, sleep maintains an oscillating pattern that reflects different levels of arousal thah has been coded as cyclic alternating pattern (CAP) (Terzano et al., 2001). Few data are available on CAP in adolescent and children (Parrino et al. 1998, Bruni et al., 2002). Our study addresses this deficiency in preschool-age children as usage of CAP would be an important adjunction to investigation of normal and pathological sleep in this age group.
Methods: CAP parameters were quantified in 10 normal healthy subjects (6 F and 4 M, mean age 4.6 years; range 3?6 years). All subjects underwent PSG recordings for two consecutive nights in a standard laboratory setting. Sleep data were stored on computer using a polysomnography digital system (Embla N7000, Medcare). Sleep macrostructure was visually scored according to the criteria by Rechtschaffen and Kales (1968); CAP was visually scored following the criteria by Terzano et al. (2001). Sleep macrostructure parameters and CAP parameters were compared with data obtained from a group of prepubertal school-age children previously published (Bruni et al., 2002). Statistical analysis was carried out using the Mann-Whitney non-parametric test.
Results: CAP rate in preschool children showed a progressive increase with the deepness of sleep, with high values during Slow Wave Sleep (SWS). Phases A1 were the most numerous (63.2%) followed by A2 (21.5%) and by A3 (15.3%). The distribution of phases A subtypes across NREM stages showed differences for the A1 subtypes that occurred more frequently during SWS than in S2 and S1. Duration of A1 phases was shorter and of A2 longer. Comparing with the older age group we found that CAP rate was lower (25.9% vs. 33.4%) mainly in NREM stage 2, while no differences have been found in NREM SWS. A1 percentage was lower while A2 (mainly) and A3 percentage was higher. We found similar values for CAP rate in SWS and for number of CAP sequences. Duration of B phases and of CAP cycles was similar to older children.
Conclusion: In the analysis of CAP and EEG arousals the maturation of EEG must be considered. In younger children the most common pattern of EEG frequency changes associated with an arousal is a shift to a more rhythmic pattern, primarily in the theta-range of EEG-frequency or, with maturation, also in the alpha range (Scholle and Schaefer, 1999; Kahn et al., 1996). Taking this into account, we considered as A2 phases also the frequency shifts > 2 seconds towards the theta range (associated or not with EMG activities). We found this EEG pattern in all preschool children analyzed and it should be considered as a stable arousal pattern typical of this age range. We suggested that A1 subtypes can have a protective role for sleep continuity and that their higher percentage in SWS could be related to restorative value of sleep, while A2 and A3, involved in the REM-on activity, could have the role of maintaining the subject arousability. The higher prevalence of A2 phases could represent a signal of higher sleep instability in this age range.

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Cerebral Impact of Childhood Sleep Apnea
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Introduction: The consequences of intermittent hypoxia and sleep fragmentation resulting from obstructive sleep apnea (OSA) on the developing brain are unknown. Investigations of childhood OSA have demonstrated effects on attention, behavior, memory, and learning, but are lim-

ited in scope. Adults with severe obstructive sleep apnea may have permanent cognitive impairment, especially involving memory. There is evidence of brain metabolite alterations measured by proton magnetic resonance spectroscopy imaging (MRSI) in adult patients. Our aim is to identify whether hypoxia or sleep fragmentation resulting from OSA is associated with 1) neuropsychological dysfunction and/or 2) alterations of normal cerebral metabolite levels measured by MRSI in age, sex, and socioeconomic matched children aged 6-16 years. We hypothesize that childhood sleep apnea is linked to impairments of neurocognitive function associated with metabolic dysfunction of the brain.

Methods: Twenty two children, (13 with severe OSA, AHI = 28.8 (SD 13.9); and 9 age matched controls) underwent 12 tests of neuropsychological function analyzing executive function, memory, intelligence, motor speed, and coordination. MRSI Methods: A PRESS sequence with a short echo time (TE 30 ms) single voxel MRS was performed in the anterior left hippocampus. Proton MRSI of the frontal white and gray matter (seven brain regions) were analyzed in five OSA patients and four controls so far. Lipid and water signals were suppressed with outer volume saturation pulses and a chemical shift-selective saturation pulse. N-acetylaspartate (NAA)/choline (Cho) ratios were calculated and compared to NAA/creatine (Cre) and Cho/Cre ratios in separate regions.

Results: There was a significant decrease in Full Scale IQ among sleep apnea patients (mean 85.2, SD 7.5) compared to age matched controls (102.6, SD 15), p <.005. There were also group differences (favoring controls) in verbal memory (California Verbal Learning Test for Children (CVLT-C) Total score p=.05), and visual spatial perception (Judgment of Line Orientation, p=.001). Parents rated children with OSA as having more symptoms of attention deficit hyperactivity disorder (ADHD) than did parents of controls (Conners Parent Rating Scale ADHD Index p <0.01. Performance measures of executive function and motor skills were not different in apnea patients compared to controls. The MRSI data demonstrated a decrease in the metabolite levels of children with sleep apnea compared to controls in the hippocampus, an area of the brain known to be vulnerable to hypoxemia, and associated with memory functions (NAA/Cho: OSA 0.91 vs. 1.18 in controls, P= 0.02). Cerebral white and gray matter showed no significant changes in apnea patients.

Conclusion: Compared to controls, children with obstructive sleep apnea demonstrate dysfunction in IQ, memory, and visuospatial perception, as well as symptoms of ADHD. Our data suggest that these neurobehavioral changes may be associated with metabolic dysfunction in the hippocampus measured by MRSI. We speculate that the neurocognitve and MRSI changes are due to intermittent hypoxia since the metabolic dysfunction occured areas of the brain that are known to be sensitive to hypoxemia. Recent studies suggest that regional variation in metabolite ratios must be considered when interpreting proton spectra of the hippocampus, therefore, our ongoing MRSI protocol will examine separate areas of the temporal lobes including both hippocampi, and the parietal lobe.

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Effects of Atomoxetine and Methylphenidate On Sleep in Children with ADHD

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Introduction: Attention-deficit/hyperactivity disorder is an early onset, neurobehavioral childhood disorder that affects 3% to 7% of school-age children in the United States. Currently, the most commonly used pharmacological interventions for ADHD are various formulations and delivery systems of the psychostimulants methylphenidate and amphetamine. Unfortunately, side effects, including insomnia and decreased appetite, and the potential for abuse can limit their use. Atomoxetine (Strattera®), a potent inhibitor of the presynaptic norepinephrine transporter, is an FDA-approved pharmacotherapy for ADHD. As a nonstimulant, atomoxetine might produce less insomnia than psychostimulants. This study compared the effects of atomoxetine and methylphenidate on the sleep of children with ADHD.

Methods: Objects were six to fourteen years old at study entry. All subjects met the DSM-IV criteria for ADHD as well as severity criteria. Subjects agreed not to use caffeinated beverages during the duration of the study. The study was a randomized, double-blind trial conducted at two outpatient sites in the United States. After collecting baseline measures, subjects were treated with each medication for about 7 weeks using a counter-balanced, crossover design with a washout period between medication periods. Parents and subjects completed diaries, subjects wore wrist actigraphy monitors to measure movement, and, in a subset of patients, polysomnography data were collected on 2 consecutive nights 3 times during the study (baseline and at the end of each medication treatment period). Polysomnography was conducted in a sleep laboratory. Efficacy was measured using the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHD RS), the Clinical Global Impressions-Severity (CGI-S) scale, the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S), and the Daily Parent Ratings of Evening and Morning Behavior-Revised (DPREMB-R).

Results: A total of 85 subjects were randomized (44 to atomoxetine then methylphenidate, 41 to methylphenidate then atomoxetine). Actigraphy data showed that, relative to baseline, there was a significant increase in time to sleep onset when subjects were being treated with methylphenidate compared with atomoxetine. Treatment with methylphenidate increased sleep onset by 30.14 minutes compared with 3.36 minutes for atomoxetine (p<.001). Atomoxetine increased actual sleep time to a greater extent than methylphenidate (10.63 versus 4.47 min for atomoxetine and methylphenidate, respectively; p=.017). Consistent with the actigraphy data, the polysomnographic data indicated that the time to onset of first sleep epoch was significantly increased relative to baseline for methylphenidate compared with atomoxetine (16.79 versus -0.31 minutes for methylphenidate and atomoxetine, respectively; p<.001). In addition, atomoxetine increased sleep efficiency relative to methylphenidate (0.01 versus -0.01; p=.020). Child diaries indicated that it was easier to get up in the morning, it took less time to fall asleep, and they slept better with atomoxetine. Parents reported that it was less difficult getting their children up and getting them ready in the morning and they were less irritable, children had less difficulty getting ready for bed, and had less difficulty falling asleep with atomoxetine.

Conclusion: The main finding was that methylphenidate significantly increased time to sleep onset relative to atomoxetine in these subjects as measured by actigraphy, polysomnography, child diaries, and parent diaries.

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Sleep of Children with ADHD Compared with Healthy Controls

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Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a central nervous system disorder that has its onset in childhood and is estimated to occur in 3% to 7% of school-age children. There is evidence that ADHD is associated with sleep problems in children. These problems include delayed sleep onset, frequent nighttime awakening, and feeling tired upon awakening. The present study used actigraphs and diaries to compare the sleep of children with ADHD and healthy controls.
Methods: Subjects were 107 children with ADHD and 46 healthy controls aged 6-14 years. Co-occurring bipolar disorder was exclusionary. Subjects participated in two sessions during which they wore actigraph watches that recorded movement. Subjects and their parents answered sleep-related questions using diaries.
Results: The actigraph data indicated no statistically significant differences in time to fall asleep. The mean number of minutes required for subjects with ADHD to fall asleep was 40.0 during the first session and 40.2 in the second session compared with 29.5 and 32.2 minutes for the control subjects (p=.215). There was a trend toward more total awake time for the subjects with ADHD. The mean number of minutes of awake time was 67.3 and 62.3 for the first and second sessions, respectively, compared with 44.8 and 40.3 for the control subjects (p=.067). The subjects with ADHD had fewer recorded movements during sleep (36.7 and 36.7 for the two sessions compared with 46.6 and 46.1 for the control subjects; p<.001). The child diaries indicated that children with ADHD had a significantly harder time getting up (p<.001), were sleepier during the day (p=.016), and slept less well (p=.009). The parent diaries indicated that children with ADHD were significantly more difficult to get up in the mornings (p<.001), had more difficulty getting ready in the mornings (p<.001), argued more in the mornings (p<.001), lost his or her temper more easily in the mornings (p<.001), had more difficulty completing tasks in the evenings (p<.001), had more difficulty sitting still during dinner (p<.001), had more difficulty playing quietly in the evenings (p<.001), were more inattentive in the evenings (p<.001), argued more in the evenings (p<.001), lost his or her temper more easily in the evenings (p<.001), had more difficulty transitioning activities in the evenings (p<.001), had more difficulty getting ready for bed (p<.001), and had more difficulty falling asleep (p<.001).
Conclusion: Compared with healthy controls, subjects with ADHD had more sleep-related problems. These problems were mainly detected using child and parent diaries.

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Sleep Problems and Cognitive Impairments in Preschoolers

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Introduction: Several studies have reported that sleep problems affect performance on cognitive tasks in school-age children. However, no study has investigated this relation in early childhood. Our aim was to evaluate the influence of sleep problems on five cognitive tasks at 2.5, 3.5 and 4.5 years of age.
Methods: This research is part of a large epidemiological study entitled Quebec Longitudinal Study of Child Development. At 2.5 years of age, 2101 children were invited to participate in this study. A randomized three-level stratified survey design was used in order to have a representative sample of infants born in 1997-1998 in the province of Quebec. Sleep measures were collected in a self-administered questionnaire filled out by the mother. For each sleep measures, the children were separated into two groups based on different criteria: 1) sleep latency (≥30 Vs <30 min), 2) number of nocturnal awakenings (≥ 3 Vs <3 awakenings), 3) total sleep time (≥ 9 Vs <9 hours) and 4) time spent awaked after sleep onset (≥ 30 Vs <30 min). Cognitive tasks such as Imitation Sorting Task (2.5 y), Blocks Task of the WIPPSI-R (3.5 y), Pairing Task (3.5 y), Memory Game (4.5 y) and Number Game (4.5 y) were performed in a face-to-face structured interview at the child's home. Chi-squares at 2.5 years and t-tests at 3.5 and 4.5 years of age were used to compare the between-group difference of mean scores on the various cognitive tasks. The differences were considered significant at p<0.05.
Results: The group of children who slept less than 9 hours (compared to more than 9 hours) had succeeded the first level on the Imitation Task in a significantly smaller proportions (68.1% Vs 74.9%; p<0.05), had significantly lower global scores on the Blocks Task of the WIPPSI-R (mean=5.08 Vs mean=6.20; p<0.01) and had reached significantly fewer levels on the Pairing Task (mean=2.57 Vs mean=3.15; p<0.03). The group of children who awakened more than 30 minutes per night (compared to less than 30 minutes) had significantly lower global scores on the Blocks Task of the WIPPSI-R (mean=5.49 Vs mean=6.41; p<0.05) and had reached significantly fewer levels on the Pairing Task (mean=2.66 Vs mean=3.22; p<0.01) and on the Memory Game (mean=4.25 Vs mean=5.13; p<0.01). Sleep latency and number of awakenings per night had no influence on mean scores of the five cognitive tasks. No differences of mean scores were shown on the Number Game (4.5 y) with any sleep problems.
Conclusion: These results suggest that preschool children who slept less than 9 hours or who awakened more that 30 minutes per night had significantly lower mean scores in specific cognitive tasks. This is of importance because the relation between sleep problems and cognitive impairments seems evolving rapidly early in life. This longitudinal study did not infer causal effects nor the mechanisms behind those outcomes. Objective sleep lab data are eventually needed to help us evaluate more precisely the relationship between sleep problems and cognitive impairments in preschoolers.

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Assessing the Validity of Night Awakenings Scored by Actigraphy with Bed-Sharing Infants

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Introduction: The use of actigraphy to assess sleep and wakefulness has increased in recent years as the technology has improved. Indeed, actigraphy has been found to yield reliable and valid sleep-wake data without the hassle and expense of laboratory assessment for adults as well as children. While multiple investigations have used the actigraph to assess the sleep-wake states of infants, no research to date has examined the validity of actigraphy with infants who share the same bed with their

parent(s). The purpose of the current investigation was to examine the validity of actigraph algorithm-scored awakenings for a group of bed-sharing infants.
Methods: Three families completed the study protocol, with infants aged 8, 11, and 15 weeks, respectively. Participants were studied for 96 consecutive hours. During this time period, mothers and infants wore MiniMotionlogger actigraphs continuously and their nighttime sleep was videotaped and scored by a trained observer using previously established methods. Actigraph records were scored using Sadeh's infant algorithm.
Results: To assess the validity of actigraph data from the bed-sharing pairs, each algorithm-scored awakening was double-checked against the video recording to assess whether the "awakenings" were truly caused by infant movements and not artifact from others in the same bed. Out of a total of 51 algorithm-scored awakenings lasting at least 2 minutes, 48 (94%) were clearly caused by the infant's movements. For one of the cases in question, it was difficult to tell whether or not the baby was awake on the videotape because his mother's body shielded him from clear view. In another, the mother picked up (thereby waking) the infant.
Conclusion: The consistent corroboration of awakenings scored from the actigraph by video observation clearly suggests the accuracy of the use of actigraphy with bed-sharing pairs to examine sleep and wakefulness. Since typical practice in previous investigations of solitary-sleeping infants and children is to disregard algorithm-scored awakenings that are under 5 minutes in duration, the fact that the vast majority of 2-minute awakenings were corroborated on video suggests that actigraphy provides a valid assessment of nighttime awakenings in a bed-sharing environment. Whether or not the scoring algorithm's distinction of active and quiet sleep is valid for use with this population is a question left to future research.

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The Effect of Body Position on Childhood Obstructive Sleep Apnea
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Introduction: In adults, obstructive sleep apnea (OSA) and snoring are worse in the supine position. In contrast, recent research suggests that prepubertal children with OSA breathe best in the supine position. These recent research findings are in conflict with our clinical experience that children's OSA is often worse in the supine position. The aim of this study was to reexamine the relationship between OSA and position in children; we hypothesized that the apnea-hypopnea index (AHI) would be highest in the supine position.
Methods: We reviewed the polysomnographic data of all children, ages 1 through 11, who underwent full-night diagnostic polysomnograms at our sleep lab between 9/99 and 9/02 for the clinical suspicion of OSA. Respiratory events were scored using standard pediatric criteria. Data from patients with chronic pulmonary disease (other than asthma) was excluded. Also excluded was data from sleep studies in which reliable positional or peak end-tidal carbon dioxide (ETPCO2) data were not obtained (peak ETPCO2 data is reported separately). One-way analysis of variance (ANOVA) was utilized to compare the AHI in the prone (P), lateral (L), and supine (S) positions in the overall group, those with OSA (defined as an AHI of at least 5.0 and at least 50% of the respiratory events being obstructive; obstructive apnea index was not calculated), and those with a body mass index (BMI) greater than 20. REM and NREM sleep data were analyzed separately.
Results: Data from 70 children was included in the analysis. In the overall group during NREM sleep the mean AHI was 6.0+/-16.0, 5.2 +/-15.2, and 5.6+/-13.6 in the P, L, and S positions, respectively. ANOVA revealed no significant differences between the groups (P=.97). In the overall group during REM sleep the mean AHI was 7.4+/-14.0, 9.5+/-15.7, and 9.7+/-17.1 in the P, L, and S positions, respectively. No significant differences were revealed by ANOVA (P=.80). ANOVA of positional data during NREM (P=.99) and REM (P=.78) of patients with OSA revealed no significant difference. ANOVA of positional data during NREM (P=.80) and REM (P=.58) of patients with a BMI greater than 20 also did not reveal a significant difference.
Conclusion: Analysis of positional AHI data did not reveal a significant difference between the P, L, and S positions in a group of children suspected of having OSA, in the subgroup of children with confirmed OSA, or in the subgroup of children with a BMI greater than 20. Our hypothesis that the AHI would be highest in the supine position was not confirmed. Limitations of this study include that the duration of apneas and hypopneas was not included in the analysis, and that many patients (N=27) did not have any prone sleep. In addition, of the nineteen children with OSA, 9 did not have any REM sleep in the supine position. In summary, we did not find a significant effect of position on respiration during sleep in a group of children who underwent polysomnography for suspected OSA.

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A Comparison of three methods for the detection of Obstructive Sleep Apnoeas and Hypopnoeas in Children
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Introduction: The efficacy of the nasal cannula (NC) was compared to the nasobuccal thermistor (NT) and the differentiated respiratory inductance plethysmography signal (DS) in detection of obstructive apnoeas and hypopnoeas in children
Methods: A single operator scored respiratory events during nocturnal polysomnographic studies three times each in consecutive children referred with possible obstructive sleep apnoea. On each occasion, either the NC, NT or DS as well as other routine channels were made visible.
Results: 11 patients (thus far) aged between 1 month and 16 years (mean 5.4 years, SD 4.3) were entered. NC was uninterpretable for more than 20% of total sleep time in 3 cases, NT in 1 case and DS in 6 cases. The time spent with an uninterpretable signal did not correlate significantly with age by any of the three methods. A total of 115 obstructive apnoeas (OA) were detected by NC, 82 by NT and 93 by DS (NS). Obstructive hypopnoeas (OH; includes mixed component) totalled 65 by NT, 56 by NC and 60 by DS (NS). The mean OAHI was 2.7 by NC (range 0-14.5), 2.2 by NT (range 0-13.3) and 2.9 by DS (range 0-14.3). The difference between the 3 methods was not significant. The strongest correlation was between DS and NC (r2=0.87; p=0.001).
Conclusion: More children had uninterpretable signals with NC and DS than with NT. Despite this, there was no significant difference between the 3 methods with respect to obstructive apnoea/hypopnoea detection. The agreement in OAHI per patient was best between DS and NC.

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Hyperactivity in Children with Asynchronous Breathing and Adenotonsillar Hypertrophy
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Introduction: Sleep disordered breathing (SDB) is a common and at times under appreciated condition affecting children. Many children with obstructive sleep apnea are reported to have behavioral problems

such as hyperactivity related to sleep disordered breathing. Prior studies have demonstrated significant reduction in hyperactivity in snoring children with and without obstructive sleep apnea (OSA) after adenotonsillectomy (T&A). We believe there are manifestations of sleep disordered breathing which have yet to be defined in children. One such condition is asynchronous (paradoxical) breathing during non-REM sleep. Adult studies have demonstrated increased non-REM asynchronous breathing in patients with upper airway resistance syndrome (UARS), as well as positional and REM-related OSA. We have postulated that increased (>10%) asynchronous breathing in non-REM sleep may represent a form of sleep-disordered breathing with an effect on behavior similar to OSA. We prospectively evaluated children with adenotonsillar hypertrophy by nocturnal polysomnography (NPSG) and by parental reports of hyperactivity, restlessness,conduct and behavioral problems by Conners' Globel Index Parent Questionaire (CGIPQ) before T&A.

Methods: Children 3 to 14 years of age referred to to an academic otolarygology center with tonsillar hypertrophy were prospectively studied by NPSG. Parents were asked to fill out a Conners' Global Index Parent Questionaire (CGIPQ) prior to the sleep study as part of the inclusion criteria. Children with circadian rhythm disorders or neurodevelopemental problems, or an obstructive apnea-hypopnea index (AHI) of > 1 apnea+hypopnea/hour during total sleep, REM sleep or supine sleep were excluded. Standard NPSG was performend in an academic sleep disorders center certified by the American Academy of Sleep Medicine. Asynchronous Breathing (ASB) was scored in minutes as parodoxical movement of the abdomen and thorax. Total minutes of ASB in REM and non-REM sleep was calculated.

Results: NPSGs were done on a total of 121 children (61% boys, 39% girls) with a mean age of 6.5 ±3 (SD) with a mean BMI of 32.3 ± 23.8 kg/m2. There was sleep disordered breathing in 49 (40%) of these, while 36 subjects either did not complete Conners questionnaires or had neurodevelopmental problems. There were 36 subjects, 20 girls and 16 boys, who met our study criteria. There was a mean age of 6.3±2.4 (SD) years with a mean BMI of 17.7±5.3 kg/m2. There was a significant Pearson correlation between hyperactivity scores and percentage of non-REM ASB (r = 0.388, p = 0.019), but not with REM ASB. There was also a correlation between BMI and % non-REM ASB (r = 0.341, p =0.045). There were 3 subjects (2 girls, 1 boy) with > 10% non-REM ASB, and they had significantly higher hyperactivity scores than those with <10% non-REM ASB (p < 0.0001). There was also a significant increase in conduct scores in the high ASB group (p = 0.0012), but not restlessness. There was no significant difference in age (5.75 ± 2.2 vs. 6.33 ±2.5 years) or BMI (26.4 ± 11.5 vs 16.9 ± 3.7 kg/m2 between those with high and low ASB. ASB during REM sleep had no significance on any parameters.

Conclusion: Asynchronous (paradoxical) breathing during non-REM sleep in children appears to be a form of sleep disordered breathing which is associated with higher hyperactivity scores on CGIPQ.

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Sleep In Prader Willi Syndrome Revisited. A Study In Young, Non Adipose Children

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Introduction: Prader Willi Syndrome is a congenital disorder characterized by neonatal hypotonia, mild retardation, short stature, hyperphagia and sleep/wake disturbances. Up to now sleep in PWS was studied in often small and inhomogeneous (age, treatment, BMI) groups of patients. These factors may have had major influence on sleep, wake and nocturnal respiration in PWS. Our study is part of an ongoing, nation wide study of various aspects of PWS in prepubertal PWS children who were diagnosed early and treated according to present day ideas since birth, and gives the baseline characteristics of sleep, wake and respiration during sleep before growth hormone therapy was started.

Methods: We studied 27 children (18 boys; age: median: 3.5 yrs; range: 1-11 yrs; BMI <27). Nocturnal sleep and respiration were recorded in a standard fashion and were scored according to the Rechtschaffen and Kales and ASDA rules. The findings were corrected for age using our own normal values or values from the literature. Daytime sleepiness was assessed by one week of continuous actigraphy.

Results: Normal values were found for time in bed and number of sleep cycles.Total sleep time was at the lower limit of normal (mean: 481 min.; SD 62 min.). Only 2 patients had sleep onset REM (SOREM) during their night sleep. The REM latency was slightly shorter than expected (mean: 70 min; SD 40 min.) Total REM duration was normal. The sleep onset latency was prolonged (mean: 33 min.; SD 22 min.). The total time in deep (SWS) sleep was low for age (mean: 120 min.; SD 31 min.). Sleep was more fragmented than in normal children with many awakenings (mean: 10/night; SD 5/night), long wake after sleep onset (mean: 49 min.; SD 33 min.) and low sleep efficiency index (mean: 80%; SD 7%). Daytime naps occurred in 21 patients, even in the older ones. Nocturnal respiration as expressed in the apnea/hypopnea index was disturbed in 25 children (AHI median: 7/hr.; range 1-19/hr.; 65% of central origin; 40% hypopneas; mean duration: 11s.; mean oxygen saturation: 95%). Leg movements were within normal limits.

Conclusion: Even after correction for factors as age, treatment and BMI that might have confounded the data from previous studies, sleep and wake in PWS children proved to be abnormal (short duration of SWS, enhanced sleep fragmentation and daytime naps). SOREMs were seen in only a few cases. Most striking were the frequent central apneas.

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Pharmacological Interventions Used in the Treatment of Sleep Disturbances in Children with Psychiatric and Neurobehavioral Disorders

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Introduction: Sleep disturbances are a prominent feature in children with neurobehavioral and psychiatric conditions. Recent surveys indicate a wide spread use of psychopharmacotherapy for behavioral problems in children with one of the primary indications being sleep disturbances. Despite the pressing needs to address symptoms of sleep initiation and maintenance problems in such children, the evidence supporting the use of pharmacological agents with sedating properties is lacking. Most of the existing practices are based on empirically derived interventions using either behavioral of pharmacological approaches without analysis of immediate and long-term treatment outcomes. The goal of this study was to examine the prevalence of use of hypnotic pharmacological agents in children with psychiatric and neurobehavioral disorders evaluated and treated at the university-based child psychiatric and neurodevelopmental disability clinics.

Methods: Parents of 384 patients (mean age 9.4± 3.9 years) attending a child psychiatric(mood, anxiety and impulse-control disorders) and developmental disabilities (pervasive developmental disorder spectrum, mental retardation) clinics completed a Childhood Sleep Questionnaire for assessment of sleep-related behaviors and treatment modalities used to help with sleep problems within the past 6 months.

Results: Most commonly used were non-prescription agents such as antihistamines (30%) and melatonin (11.5%). Among prescription med-

ications, alpha-agonists (clonidine) were the most frequently prescribed agents (17.5%), followed by atypical antipsychotics (6.2%), trazadone (6%) and tricyclic antidepressants (5.8%). Benzodiazepines were the least recommended medications by physicians for sleep problems in children. Approximately half of the parents reported these medications as being helpful in inducing sleep and helping with sleep maintenance.
Conclusion: Results of the survey indicated a high rate of use of both prescription and nonprescription medications for sleep problems among parents of children with psychiatric and neurobehavioral disorders. Further research in needed to develop a rational approach to the use of psychopharmacological agents in children with special needs.

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Psychiatric Symptoms in Children with Insomnia Evaluated at the Pediatric Sleep Medicine Center

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Introduction: It has been established that approximately 35% of adult insomniacs suffer from an underlying psychiatric disorder, and that insomnia serves as an early marker and a major risk factor for development of depression. Recent studies of sleep problems in children have indicated that between 13.2% and 28.6% of children who report trouble sleeping exhibit symptoms of anxiety and depression.These findings have raised an important question of insomnia as either a first sign of emotional distress or an actual cause of mood disturbance in susceptible individuals whose sleep homeostasis is poorly preserved by intrinsic biological mechanisms and can be impaired at an early age. The mail goal of this study was to evaluate clinical and psychiatric symptoms in children with insomnia whose other sleep disorders and associated medical conditions have been ruled out by the sleep medicine specialist and nocturnal polysomnography.
Methods: Retrospective chart review of children referred to the pediatric sleep medicine was conducted. Children presenting exclusively with sleep initiation and/or maintenance problems underwent clinical psychiatric interview and their parents have completed the Behavioral Assessment System for Children (BASC), Pediatric Symptom Checklist (PSC), the Clinical Attention Problem Scale (CAPS) and a detailed sleep questionnaire.
Results: Fifty percent of children with persistent insomnia had a professional diagnosis of another psychiatric disorder. Among the other half of the children with insomnia whose parents denied previous psychiatric history, 40% displayed psychiatric symptoms as documented by psychometric measures and clinical interview. Strong correlation was observed between longer sleep onset latency and shorter REM sleep latency on polysomnography and depressive BASC scores.
Conclusion: Majority of children presenting with persistent insomnia exhibit clinical symptoms of psychiatric disorder. Additional psychometric assessments are warranted when evaluating children and adolescents with symptoms of sleep initiation and maintenance insomnia.

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Long-Term Melatonin Treatment For Sleep Disorders In Autistic Children. A Two-Year Follow-Up Study

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Introduction: Severe and persistent sleep disturbances have been reported in autistic children. However, the majority of studies have been carried out on heterogeneous groups. Therefore, we undertook this study to evaluate the prevalence of sleep problems in a selected sample of autistic children without other coexisting pathology, and to determine the effect of long-term controlled-release melatonin (CR) treatment on sleep disorders. The study was designed to prospectively evaluate the effectiveness of CR melatonin administered openly over a period of up to 24 months.
Methods: Out of 56 children meeting inclusion criteria, 29 were enrolled in a 2-y open-label study. Diagnosis was based on DSM IV criteria and Childhood Autism Rating Scale score above 29.5 (Schopler, 1980). To assess baseline sleep, we used Children's Sleep Habits Questionnaire (CSHQ, Owens 2000) Moreover, parents completed a sleep diary. Baseline sleep variables, CSHQ scores were compared with sex and age-matched controls. Children were rated by CSHQ at baseline and after scheduled intervals: 1, 3, 6 months (end of treatment), 7 months (1 month after discontinuation), 12 and 24 months (reintroduction of treatment, if necessary). After baseline, children were given a 3 mg CR melatonin orally prior to bedtime. For longitudinal analyses, we used Rm-ANOVA, covaring for age, sex and IQ.
Results: Twenty children (18 M, 2 F aged 2.6-9.1 yr) completed the study. Clinical interview confirmed a high prevalence of sleep problems in autistic children (difficulty settling to sleep 18/20, long-lasting night waking 13/20, and seasonal changes in sleep problems.3/20). Moreover, cosleeping was reported by 65% of autistic children compared to 5 % of controls (chi square <.001). Autistic children scored significantly more than controls at CSHQ (66.9 vs. 38.4; p<.001). Bedtime was significantly later (23.15 vs. 22; p<001), while no significant differences were found regarding risetime. Moreover, autistic children slept significantly less (410 vs 610; p<.001). Rm-ANOVA results in CSHQ total and subdomains scores revealed long lasting positive melatonin effect. During treatment sleep patterns of all children improved. Rm-ANOVA results showed a significant reduction of bedtime resistance (p<.001) an increase of sleep duration (p<.001), a decrease of number and duration of nightwakings (p<.001) over time. One month after discontinuation, 16 children returned to pre-treatment sleep score, whereas in 4 cases improvement persisted. Therefore, we decided to prescribe 6 months of melatonin treatment periods with two-week interval free in 16 patients, whose sleep problems returned to baseline. All 20 patients were revaluated at 1 and 2-yr from the beginning of the study. In 1 and 2-yr follow-up visits, continuers showed a significant and long lasting improvement of sleep pattern (discontinuation vs 1- and 2 yr: 63 vs 44; <. 001), the non-continuers maintained the improvement obtained. No adverse side effects were reported
Conclusion: Results highlight that assessment of sleep in autistic children need particular attention, because of the high prevalence, persistence and severity of the problem. Our long term follow up study underlines that CR melatonin may provide an interesting safe and well-tolerated treatment for sleep disorders in autistic.

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Sleep Hygiene In Italian Preschoolers And School-Aged Children

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Introduction: Sleep hygiene refers to a list of behaviors, environmental conditions and other sleep-related factors that can affect sleep initiation and maintenance. Previous research has demonstrated that poor sleep hygiene is associated with sleep problems and that good sleep hygiene

improves sleep patterns in adults and young adolescents. Despite the importance of these findings, few studies investigated sleep hygiene in children. The purpose of this study was (a) to describe sleep hygiene practices in healthy preschoolers and school-aged children and (b) to investigate the relationship between sleep hygiene and sleep behavior in this age span.

Methods: Data were collected on 818 healthy children (51.5% male), aged.4.1-10.11 yr (M=7.5, SD 2) attending ten public schools in Rome (response rate =79.5%). For the purpose of establishing a developmental picture, the sample was divided into three age groups (4-6, 6.1-9; 9.1-10.11 years).Parents completed the Children's Sleep Hygiene Scale (CSHS, Harsh et al., 2001) and the Children's Sleep Habits Questionnaire (CSHQ, Owens et al., 2000). CSHS is a 25-item assessment of sleep hygiene practices. It provides a total scale score, with higher scores indicating better sleep practice of sleep hygiene . The CSHQ, examines sleep behaviors in children and includes items relating to a number of key sleep domains that are grouped into 8 subscales (Bedtime Resistance; Sleep Onset Delay; Sleep Duration; Sleep Anxiety;Night Wakings; Parasomnias;Sleep Disordered Breathing; Daytime Sleepiness). Higher scores indicate more sleep problems. In this study, the CSHS and CSHQ showed adequate internal consistency (Cronbach's alpha .73 and .87 respectively).

Results: The CSHS showed practice of poor sleep hygiene across al age groups. Particularly 11% of children were reported to habitually drink caffeinated beverages before bedtime, and almost 40% used their bed for things other than sleep (watching TV, playing videogames etc). These sleep practices were more evident in the oldest group. Two-way ANCOVA (age groups and sex as independent factors) indicated a significant main effect on sleep hygiene only for sex [$F(1,8)=15,11$ $p<.001p < 0.001$]. Interaction between the two was also significant [$F(2,8)=3,94$ $p<.05$)]. Females reported much better sleep hygiene only in the oldest group (Scheffe'post-hoc: 123,8 vs 116,8; $p<.01$). SES as covariate showed a significant effect (beta= .11; p=.005) indicating that higher SES acts as protective factor. As expected, a strong negative linear correlation was found between the CSHS and CSHQ total scores (r= -.34; p<001) and its subscales (in particular: bedtime resistance r=-.28; p<001; sleep onset delay r=-.30; p<001; sleep duration r=-.36 ; p<001 and daytime sleepiness r=-.39; p<001).

Conclusion: These results suggest that poor sleep hygiene practices are common in Italian children. This study indicated that sleep hygiene is importantly related to sleep problems mainly to bedtime difficulties and sleep duration. Probably, as a consequence, it is strongly correlated also to high level of daytime sleepiness. Further studies are needed to better understand this relationship and to determine if good sleep hygiene practices may improve sleep quality and quantity, reduce daytime sleepiness, and prevent some sleep problems in childhood.

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Comparing Subjective and Objective Measures of Sleep in Child Depression

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Introduction: Children and adolescents with Major Depressive Disorder (MDD) often report high rates of sleep disturbances; yet, polysomnographic studies have often failed to find objective evidence of these disturbances. In order to examine the relationship between subjective and objective sleep variables, we compared subjective sleep reports of children and adolescents with MDD and healthy controls who underwent comprehensive clinical and polysomnographic assessments.

Methods: Fifty-one MDD and 42 healthy subjects, ages 8-17, participated in a comprehensive psychobiologic study that included three nights of EEG sleep. All subjects were studied medication-free and had undergone a full medical and psychiatric evaluation. Subjective sleep measures were obtained each morning, as subjects completed a post-sleep form indicating the subjective evaluations of their sleep, which corresponded with polysomnographic studies. The subjective rating indicated subjective sleep quality (0 = very bad sleep to 100 = very good sleep), subjective ease of waking (0 = very difficult to wake up to 100 = very easy to wake up), subjective experience of minutes until falling asleep, number of times awake during the night, total minutes awake during the night, time of going to bed, trying to fall asleep time and good morning time. These subjective ratings were then compared to the objective sleep variables gathered through standard polysomnographic recording.

Results: Depressed subjects report significantly worse sleep on three self-report scales subjective sleep quality ($F(1,89)=15.3$, $p\leq.01$), perceived ease of waking in the morning ($F(1,89)=11.7$, $p\leq.01$), and subjective minutes awake in the night ($F(1,81)=5.8$, $p\leq.02$). In contrast, the EEG measures indicated no objective evidence of sleep difficulties or disruptions in the depressed sample. There were no significant group differences in total sleep, stage 1,2,3,4 REM, or REM latency. EEG measures of night waking showed, paradoxically, that depressed children tended toward having less sleep disruption than the controls. In order to examine this further, we performed additional analyses by selecting the depressed children (n=12) with the most severe ratings of subjective sleep disturbances and comparing their EEG data with the controls. Again these results revealed a paradoxical pattern of less awake time. These depressed subjects with the greatest sleep complaints had fewer EEG awakenings at night (Night 1: Control: 15.5 ±5.7, MDD: 13.7 ±5.3, Night 2: Control: 16.5 ± 5.5, MDD: 11.8 ± 4.8, $F(1,52)=3.8$ $p\leq.06$). and fewer minutes awake during the night compared to the normal control group. (Night 1: Control: 40.2 ± 26.5, MDD: 23.8 ± 17.6, Night 2: Control: 27.4 ± 13.7, MDD: 13.5 ± 9.2, $F(1,52)=8.8$, $p\leq.01$).

Conclusion: As reported in previous studies, these data show clear evidence of subjective sleep complaints in the depressed children. However, the EEG data in these same depressed children on the same nights as when reporting highly disrupted sleep, showed that they slept as well or better than the normal controls. Further, the MDD children with the greatest sleep complaints had significantly less awake time than the normal controls. These findings raise several provocative questions regarding the source and nature of sleep complaints associated with early-onset depression.

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Ethnic Variation in Childhood Sleep Characteristics

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Introduction: Recent epidemiological studies in both adults and children have established ethnicity as a risk factor for sleep-disordered breathing (SDB). Indeed, African American children have been reported to be 3 times more likely than Caucasian children to have SDB. Nonetheless, despite recent studies focusing on the differences in frequency of respiratory events between African American and Caucasian populations, sleep architecture and other sleep parameters have not been reported. The aim of this study, therefore, was to report sleep characteristics in African American and Caucasian children recruited from a community cohort.

Methods: A sleep habits questionnaire was distributed to the parents of all children attending public first grade classes in the greater Louisville area. From the responders, parents of snoring and non-snoring children were randomly contacted and their children were invited to undergo an

overnight polysomnographic evaluation (PSG) in the sleep laboratory as part of a larger study.
Results: A total of 2370 questionnaires were received, of which 2069 pertained to children of either African American or Caucasian background. The responses to these 2069 questionnaires were analyzed and 393 first-graders underwent PSG evaluation. From the questionnaires, there were several subjective differences in reported sleep habits; African Americans were less likely to go to bed willingly, and more likely to report snoring, struggling to breathe, morning headaches, and daytime sleepiness ($p<0.001$ for all variables). Of those children who underwent PSG evaluation 25% were African American, which reflects the ethnic make-up of the local population. Mean age was 6.6 ± 0.5 years for each group and there were a similar proportion of males (52% males in the African American group and 57% males in the Caucasian group). No differences between ethnic groups were observed for sleep latency, total sleep time, sleep efficiency, REM latency, or any of the sleep stages. However, African American children had significantly fewer spontaneous arousals (7.1/hr vs. 8.3/hr; $p=0.02$) and significantly more respiratory arousals (4.1/hr vs. 1.4/hr; $p=0.001$). African American children also had a higher AHI than Caucasians (3.7 vs. 1.3; $p<0.0001$) with lower nadir oxygen saturations (88.3% vs. 92.0%; $p<0.0001$). Furthermore, we found that Caucasian children had more periodic leg movements (PLMs) during sleep (2.8/hr vs. 1.3/hr in African Americans; $p<0.0001$).
Conclusion: In a community cohort parents of African American children report more sleep problems than those of Caucasian children. Moreover, on PSG evaluation African Americans have more respiratory disturbances and related arousals while sleep latencies and sleep stages remain similar to Caucasians. However, PLMs were significantly more prevalent in the Caucasian race. The reason for this difference is currently unknown.

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Melatonin For Sleep-Wake Schedule Disorders In Young Children
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Introduction: The literature dealing with Delayed Sleep Phase Syndrome (DSPS) and melatonin treatment in the pediatric age group is limited. We present retrospective data regarding clinical follow-up and melatonin treatment in young children with DSPS.
Methods: 29 children, aged 5.6 to 12.2 years (9.3 ± 2.1 years), 9 girls and 20 boys, were diagnosed as having DSPS, on clinical ground and by actigraphy of one week duration in non-restricted daily schedule, regarding sleep time or waking up hours.
Results: 29 (100%) children reported difficulties in falling asleep at bedtime, 23 (79%) in waking up. 21 (72%) of the children were reported to have socio-behavioral problems with their peers, poor school attendance, reduced attention span and low academic achievements. 16 (55%) had excessive daytime somnolence. 19 (66%) were diagnosed as having attention deficit hyperactive disorder (ADHD) or exhibited an ADHD like behavior. Melatonin was given to 21 of the children, doses ranged between 1mg to 6 mg (4 ± 1.3 mg) (n=21), for a total period of 5.9 ± 3.9 months. No side effects were observed, apart from 3 children complaining of drowsiness that resolved later. On melatonin vs. pre melatonin falling asleep time (21:26 ± 0:52 vs. 23:18 ± 1:16; $p<0.001$), and sleep duration (9.4 ± 0.9 hrs vs. 7.7 ± 1.2 hrs; $p<0.001$) improved significantly. Interestingly, sleep duration on melatonin reached the same values as sleep duration in the week with non restricted daily schedule (9.4 ± 0.9 hrs vs. 9.1 ± 0.9 hrs, accordingly). Other symptoms such as school attendance, performance and behavior improved substantially in 19 of the 21 children who had taken melatonin (91%). Stopping melatonin therapy in the summer vacation did not result in any untoward effects, but, falling asleep difficulties recurred in 11 out of 15 (73%), and treatment was resumed when school restarted. Most parents and children expressed their satisfaction from the treatment, and complied accordingly.
Conclusion: A substantial number of children with DSPS suffer from socio-behavioral and school problems. Melatonin seems to be efficacious and safe in treating children with DSPS and improves the related problems.

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Differential Expression of Inflammatory Mediators in Exhaled Breath Condensates of Children with Obstructive Sleep Apnea Syndrome
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Introduction: Upper airway inflammation is now being recognized in adults with obstructive sleep apnea syndrome (OSAS). However, the role played by eicosanoids such as leukotrienes and prostaglandins is unclear. The aim of this study was to investigate whether eicosanoids are measurable in exhaled upper airway breath condensates (EBC), and to determine if differences in these inflammatory mediators emerge among children with and without OSAS.
Methods: EBC were collected from 18 children undergoing overnight polysomnography. Prostaglandin E2 levels (PGE2), Leukotriene B4 (LTB4), and Cys-Leukotrienes (Cys-LT C4/D4/E4) were analyzed using commercially available ELISA assays. Children were assigned to SDB (OAHI>5) or to control group (OAHI<1).
Results: LTB4 levels were elevated in children with an AHI>5 (range 3.3-5.7 pg/mL) compared to control children (range 2.2-5.1 pg/mL; $p<0.05$). Similarly, Cys LT (LTC4/D4/E4) were also increased in SDB (31.0-79.8 pg/mL vs. 17.4-67.5 pg/mL, $p<0.05$). In contrast, PGE2 concentrations were similar in the 2 groups (range 1.92-3.77 ng/mL and 1.95-4.56 ng/mL, respectively; $p=0.53$).
Conclusion: Inflammatory mediators such as leukotrienes and prostaglandins can be readily quantified in exhaled breath condensates of the upper airway in children. Selective increases in Leukotrienes (B4 and C4/D4/E4) are present in children with OSAS, suggesting a potential role in the pathophysiology of upper airway dysfunction, presumably via increases in neutrophil migration and upper airway inflammation. If confirmed, leukotriene modifiers may serve as a potential pharmacological target aiming to decrease the inflammatory cascade in the upper airway of children with OSA.

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The Adenoid Puzzle: Size Does Matter in Children with OSA
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Introduction: Obstructive sleep apnea (OSA) in children is clearly associated with enlargement of adenotonsillar tissue. Although OSA will resolve in 85% of children undergoing tonsillectomy & adenoidectomy (T&A), previous studies failed to show significant correlation between the degree of improvement and that of anatomical impairment.
Methods: 17 children with OSA who underwent T&A as well as pre-

and post-T&A polysomnographic evaluation were studied. The pre-operative size of the adenoid tissue was determined from lateral neck X-rays and expressed as the ratio of maximal adenoid diameter/nasopharyngeal airway diameter (AD/NP). The changes (Δ) in obstructive AHI, total (TAI), spontaneous (SAI), and respiratory (RAI) arousal indices, as well as the newly reported Sleep Pressure Score (SPS), were correlated with AD/NP.
Results: Significant correlations were present between ΔAHI, ΔTAI, and ΔRAI and AD/NP ($r=0.53$, 0.52, and 0.50 respectively; $p<0.05$). Furthermore, Δ SPS was closely correlated with the relative size of the adenoid tissue in these children ($r=0.65$; $p<0.01$).
Conclusion: The polysomnographic response to surgical removal of enlarged tonsils and adenoids is dependent on the relative size of the adenoid tissue and is more likely to improve with increasing degree of nasopharyngeal obstruction.

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Normative Values for Polysomnography in Children
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Introduction: Overnight polysomnography (PSG) is the gold standard for the diagnosis of sleep-disordered breathing (SDB). Despite a wealth of data from adult studies, normative reference values for sleep architecture in young children are limited. Thus, we sought to describe a reference range for sleep parameters in normal healthy children without evidence or history of sleep disturbance.
Methods: A detailed sleep habits questionnaire was distributed to the parents of 3–8 year old children in the Louisville metro area. Questions included "How often does your child snore?" and "Does your child have difficulty going to sleep?" Response options included "Never" (never in the past 6 months), "Rarely" (once a week), "Occasionally"(2 times a week), "Frequently" (3-4 times a week), or "Almost Always" (more than 4 times a week). Children with snoring or difficulty initiating sleep reported as "Never" or "Rarely" were invited to participate in a standard overnight PSG providing that they did not suffer from any craniofacial or other congenital abnormalities. Children with attention deficit/hyperactivity disorder were also excluded and all children were free of medication at the time of PSG.
Results: A total of 153 normal healthy children underwent PSG assessment. Two of these children were found to have SDB and were excluded. Thus 151 children were included in the total sample. The mean age of the sample was 6.2 years (range 3.4–8.3 years) and 76 were boys (50%). The majority of the sample (71%) were Caucasian, reflecting the ethnic distribution of the local population. Values are presented as mean ± SD. Sleep time was 7.8 ± 0.9 hours with sleep latency of 26.6 ± 26.0 min and REM latency of 109.6 ± 51.9 min. Sleep efficiency was 88.9 ± 7.6%. Sleep architecture was distributed as follows: 7.1 ± 5.0 % (Stage 1); 42.9 ± 7.8% (Stage 2); 25.5 ± 4.4 (delta sleep); 24.3 ± 5.3 (REM sleep). Mean spontaneous arousal index was 7.8 ± 3.4 with respiratory arousal index being 0.8 ± 1.5 and a total arousal index of 9.0 ± 3.6. Periodic leg movement index was found to be 2.5 ± 3.7 and AHI was 0.7 ± 0.7. Mean oxygenation was 97.7 ± 0.9% while the saturation nadir was 93.0 ± 3.6%.
Conclusion: This study provides normal values for commonly used polysomnographic parameters in healthy children between the ages of 3 and 8 years. These values will be useful as future reference values during PSG assessment in young children.

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Sleep and Suicidal Behavior: A Cross-Sectional Study of Adolescents in China
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Introduction: Suicide represents a major worldwide social and public health problem with about one million deaths in the world each year. It is among the top three causes of death in adolescents and young adults. Suicide risk begins to increase during adolescence and is associated with multiple psychosocial and biological factors. There is consistent evidence that adolescents do not get enough sleep and that their sleep patterns are characterized by staying up late. Adolescents are also at great risk for sleep problems such as insomnia and circadian rhythm sleep disorders. However, little is known about the relationship between sleep and adolescent suicidal behavior with community samples.
Methods: This study represents one part of an epidemiological project on mental health problems among rural adolescents of Shandong Province, China (Liu et al., 2000). From a total of 1,400 adolescents who were sampled from three middle and two high schools, 1,362 returned their questionnaires with complete data for analysis (60% boys, mean age = 14.6 years). The questionnaire included two questions asking about suicidal ideation (I think about killing myself) and suicide attempts (I deliberately try to hurt or kill myself) and 7 questions with regard to sleep behavior (i.e., bedtime, sleep duration, insomnia symptoms, nightmares, and hypnotic use). Multivariate logistic regression analyses were conducted to examine the association between sleep behavior and suicidal ideation and suicide attempt, respectively.
Results: Overall, 12.3% of the sample reported having suicidal ideation, 7.0% having suicide attempts in the past 6 months, 17% having insomnia symptoms, and 2.3% having taken hypnotic medication in the past month. Average sleep duration of this sample was 7.6 hours (SD = 0.9) and decreased with age. Logistic regression analyses showed that short sleep duration (< 8 hours a day) (OR = 1.42, 95% CI = 1.01, 2.01), nightmare (OR = 1.37, 95% CI = 0.97, 1.97), and insomnia (OR = 1.31, 95% CI = 0.87, 2.01) were associated with increased risk for suicidal ideation after adjustment of age, sex, occupation of the father, and depressive symptoms. For suicide attempts, the following sleep behaviors remained significant in the multivariate logistic regression model: short sleep duration (OR = 1.83, 95% CI = 1.10, 3.06), nightmare (OR = 2.54, 95% CI = 1.46, 4.42), and insomnia (OR = 1.64, 95% CI = 1.00, 2.82).
Conclusion: This investigation represents one of the few studies on the relationship between sleep and suicidal behavior with a community sample of adolescents. In our study, short sleep duration, nightmare and insomnia were associated with increased risk for suicidal ideation or suicide attempts. One mechanism responsible for this possible association between sleep and suicide could be the role of serotonin (5HT), because serotonergic function has been found to be low in patients who attempted and/or completed suicide, and serotonin has also been documented to play an important role in onset and maintenance of slow wave sleep and in REM sleep. Further studies are needed to investigate the causal link between sleep disturbances and adolescent suicidal behavior.

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Respiratory-Related Evoked Potentials During Sleep in Children

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Introduction: Respiratory-related evoked potentials (RREPs) are used to study cortical responsiveness to increases in ventilatory effort. RREPs are obtained by briefly occluding the airway during inspiration. RREPs in children during wakefulness have a similar waveform to those seen in adults. During sleep in adults, the early RREP components are preserved and two large negative peaks are seen (N350 and N550). This present study was conducted to investigate RREPs in children during the various stages of sleep. We hypothesized that the RREPs of children during sleep would be similar to those of adults.
Methods: Six, healthy, non-snoring prepubertal children (one female) were recruited from the general population. The subjects underwent a baseline polysomnograph to rule out sleep-disordered breathing. On a separate night, a second polysomnograph was done and RREPs were measured. EEG electrodes were placed at Fz, Cz, Oz, C3, C4, A1, and A2 based on the international 10-20 system, and were connected to a Neuroscan system. EEG activity was recorded continuously and later analyzed offline. The subjects breathed through a full face mask, with a positive bias flow of 4 cm H20. The mask was attached to an inspiratory occlusion valve. Multiple (150-200) inspiratory occlusions of 400 msec duration were each performed during stage 2, slow wave (SWS), and REM sleep. Each occlusion was separated by at least 2 non-occluded breaths. RREPs were determined and averaged for each trial per stage of sleep. Peak latencies and amplitudes were determined and analyzed for effect of electrode site with either ANOVA or t-tests.
Results: RREPs were obtained for all subjects during stage 2 and SWS, and for 5 subjects during REM sleep. The stage 2 RREP contained a series of prominent components in all subjects. P2 ($p<0.01$), N350 ($p<0.05$), N550 ($p<0.05$) were all significantly larger at Cz. A late positive component (at approximately 1200 ms) was more evenly distributed over the scalp. The SWS RREP was very different from adult data, with a less prominent N550 component which was only reliably seen at Fz, and N350 ($p<0.01$) and P900 ($p<0.01$) components significantly larger at Cz. The REM RREP was most similar to that seen in adults, with prominent P2 and N350 components, but restricted to frontal and central sites with similar amplitudes at each site.
Conclusion: This is the first study to investigate RREPs during sleep in children. The RREPs during sleep were markedly different from what has been previously described in adults. Children do not have the frontal dominance of N550 during stage 2 seen in adults. During SWS, the N550 is only present in the frontal sites, is substantially smaller than that seen in young adults, and is essentially absent at other sites. During REM sleep, RREPs in children have a dominant fronto-central N350, similar to adults. We speculate that the difference in the pattern of responses during non-REM sleep in prepubertal children compared to adults is due to the substantial proportions of high amplitude delta activity present in childhood, and the role of delta EEG in the production of sleep evoked potentials.

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Narcolepsy Cataplexy: Clinical Efficacy Of High Dose Intravenous Immunoglobulins In A 10-Year-Old Boy

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Introduction: Recent studies suggest that clinical manifestations of narcolepsy might occur once CSF hypocretin levels are undetectable, that a putative immune process targets hypocretin neurons with irreversible damage, and that immunosuppressive treatments are ineffective even near the onset of narcolepsy.
Methods: A 10-year old boy was seen 2 months after the onset of cataplexy, excessive sleepiness and irresistible naps. No triggering factor could be identified except for increased appetite and substantial weight gain. Typical narcolepsy-cataplexy was diagnosed with normal neurological and psychiatric examinations. No family history of any diagnosed sleep disorder could be documented. The HLA typing was positive for DQB1*0602/0301. Standard brain MRI did not reveal any lesion. CSF hypocretine-1 level was below the detection limit. Genomic sequencing of the prepro-hypocretin and its 2 receptor genes did not reveal any mutation. Intravenous immunoglobulin g (IVIg) perfusion at 1g/kg/day for 2 consecutive days was initiated and followed by Prednisolone 1.3 mg/kg/day for 3 weeks.
Results: A single partial cataplexy was reported 3 days after IVIg and sleepiness was improved. Not a single cataplexy or irresistible nap was reported during the next 3 weeks. Parents reported dramatic improvement which was confirmed by the absence of irresistible naps and falls. The prednisolone dosage was reduced to half daily for 3 weeks. A second CSF hypocretin-1 measurement indicated still undetectable levels. Only 6 partial cataplexies of the face were noticed during the 2 months following the IVIg treatment with a tendency for gradual increase in daytime sleepiness.
Conclusion: This is the first report illustrating the clinical efficacy of high dose IVIg in narcolepsy. If confirmed in controlled trials with objective measures of sleepiness, this finding strongly suggests that the immune-mediated part of narcolepsy symptoms is independent from hypocretin deficiency. Thus, IVIg might constitute a treatment of choice because of lack of efficacy and poor tolerance of corticosteroides.

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Sympathetic Activity in Children with Congenital Central Hypoventilation Syndrome

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Introduction: Congenital Central Hypoventilation Syndrome (CCHS) is a genetic disorder characterized by failure of automatic control of breathing in the absence of obvious anatomic lesions. Such patients show dysfunction of the autonomic nervous system (ANS), suggested by reduced heart rate variability and abnormal circadian blood pressure patterns. Pulse Arterial Tonometry (PAT) is a noninvasive beat-to-beat technique (finger-mounted probe) that is exquisitely sensitive to changes in sympathetic autonomic nervous system tone and is thus an ideal tool to examine dynamic ANS responses in children with CCHS and their families.
Methods: Cold hand pressor tests were performed in 19 children with CCHS and 31 parents (17 mothers). Twelve healthy control children also underwent the same test. The left hand was immersed in ice cold water for 30 seconds while PAT signal was continuously monitored during

immersion and recovery periods in the right hand. Changes in PAT signal amplitudes were calculated by averaging the mean amplitude over a 10-sec period before the pressor test (baseline), during the test (challenge), and immediately following removal of the hand from the water (post challenge), and then at 30 second intervals during the recovery phase. Amplitudes were expressed as % change from corresponding baseline.
Results: All subjects showed sympathetic discharge-induced attenuation from baseline when their hand was immersed in ice cold water. Mean attenuations from baseline values were: CCHS 52.5 ± 19.1%; Mothers 47.7 ± 20.7%; Fathers 47.6 ± 19.2%; Control children 77.3 ± 11.5%. No differences in sympathetic discharge-induced attenuation of PAT signal were evident between the children with CCHS and either parent. However, both CCHS children and their parents had significantly smaller attenuations than controls ($p<0.001$). Moreover, within 60 seconds of removing the hand from the ice water, the amplitude of the PAT signal had returned to baseline for the children with CCHS and their parents while the signal amplitude of the control children remained significantly attenuated for longer periods of time during recovery ($p<0.001$). In addition, the PAT amplitude from the children with CCHS showed the largest variability while the signal amplitude from the control children showed the least variability.
Conclusion: Children with CCHS show an attenuated response to sympathetic stimulation. These findings support a role for altered ANS regulation in CCHS. Furthermore, changes in the ANS are also manifest in parents of CCHS children, suggesting possible genotype-phenotype relationships.

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Respiratory Cycle-Related EEG Changes (RCREC) Predict Neurobehavioral Outcomes In Childhood OSA

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Introduction: Neurobehavioral symptoms, such as sleepiness in adults and hyperactivity in children, are common in sleep-disordered breathing (SDB). However, rates of phenomena believed to contribute to these symptoms—such as apneas, hypopneas, and arousals—may not predict neurobehavioral outcomes well. Recent development of a new EEG signal analysis algorithm permitted demonstration of respiratory cycle-related EEG changes (RCREC) during non-apneic sleep of 10 children with and without SDB. Delta-range (1 - 4 Hz) RCREC showed promise as a correlate of objectively-measured daytime inattention and sleepiness. We have now studied the predictive value of RCREC and standard SDB measures in a new group of children evaluated before and one year after adenotonsillectomy.
Methods: Subjects were 34 children, 19 boys and 15 girls, aged 8.6 ± 1.9 (s.d.) years (range 5.5 - 12.5) at study entry. Nocturnal polysomnography and neurobehavioral evaluations were performed before and after adenotonsillectomy that had been scheduled for any clinical indication. Obstructive sleep apnea was defined by a pediatric (2-breath, thermocouple-derived) obstructive apnea index >0.5. The computer algorithm divided non-apneic respiratory cycles in the first 3 hours of recorded sleep into 4 time segments, as defined by airflow maxima, minima, and their midpoints. Delta-range EEG power for each time segment was computed using the short-time Fourier transform on data recorded at one central lead. Power for each segment was normalized to the power for the whole respiratory cycle, and results were averaged over about 2,500 cycles. The maximum difference between mean segment powers was defined as a subject's RCREC. Pre-operative RCREC were tested for correlation with post-operative changes in hyperactivity and sleepiness. Hyperactivity was assessed by a Behavioral Index, defined as the average of relevant scales from the Conners' Parent Rating Scales and the Child Symptom Inventory-4. Sleepiness was assessed by Multiple Sleep Latency Tests.
Results: Pre-operative delta-range RCREC predicted improvement in behavior (Spearman rho = 0.36, p = 0.036) whereas the apnea/hypopnea index and the visually-scored arousal index did not (rho = -0.30, p = 0.088; rho = -0.21, p = 0.238, respectively). In the subgroup of 16 children with obstructive sleep apnea, the association between baseline RCREC and improvement in the behavioral index was stronger (rho = 0.68, p = .004), whereas the apnea/hypopnea and arousal indices again were not predictive (rho = -0.04, p = 0.88; rho = 0.18, p = 0.504). Similarly, among the 34 adenotonsillectomy subjects, improvement in sleepiness on the Multiple Sleep Latency Test was predicted by initial delta RCREC (rho = -0.41, p = 0.015), but not by apnea/hypopnea or arousal indices (rho = -0.09, p = 0.615; rho = -0.03, p = 0.882).
Conclusion: Delta-range RCREC predict neurobehavioral responses to adenotonsillectomy in children, many of whom have SDB. In contrast, rates of apneic events and arousals do not predict responses well. These data suggest that RCREC have clinical utility. We speculate that the RCREC represent brief but numerous cortical microarousals that could mediate effects of SDB on daytime behavior and sleepiness.

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Relationship of Sleeping and Waking Bout Frequencies and Lengths to the Development of Behavioral States in Preterm Infants

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Introduction: This study described the development of sleeping and waking during the preterm and early post-term periods and determined the extent to which developmental changes were due to changes in the mean length or frequency of state bouts.
Methods: The sample, 133 preterm infants (71 boys, 62 girls; 69 Whites, 62 African Americans, 2 Asians) who weighed less than 1500 gm or required mechanical ventilation, was recruited from three hospitals in three states. Mean gestational age at birth was 28.8 weeks; mean birth weight was 1217 gm. Weekly 2-hour observations during a daytime, inter-feeding period were conducted from the time infants were no longer critical until 43 weeks post-conceptional age or discharge. A single follow-up observation was conducted 1-3 months later. During the observation, the occurrence of five behavioral states were coded every 10 seconds. Only observations containing at least 1 hour of sleep were used in analyses in order to focus on state patterns within a sleep period. A state bout was defined as a continuous run of a state lasting at least 30 seconds. General linear mixed models were calculated for the total amount of each state, the frequency of each state bout per hour, and the mean length of each state bout using the linear and quadratic effects of post-conceptional age as predictors and hospital, gender, race, birth weight, theophylline treatment, length of mechanical ventilation, frequency and amount of caregiver touches, and the interactions of these variables with post-conceptional age as covariates.
Results: The total amount of active sleep decreased with age primarily due to a decrease in active sleep bout frequency. The mean length of

active sleep bouts decreased before term but increased after term. The overall amount of quiet sleep increased primarily due to an increase in bout lengths. Quiet sleep bout frequencies increased until term and then decreased. The total amounts of quiet and active waking increased with age. Quiet and active waking bout frequencies increased with age until term and then decreased, whereas the mean length of quiet and active waking bouts decreased until term and increased after term. The total amount of sleep-wake transition increased until term and then decreased. The mean length of sleep-wake transition bouts increased over the preterm period, whereas bout frequencies showed a curvilinear decrease. The covariates had minor effects on developmental patterns. Caregiver touches increased sleep-wake transition bout lengths and the frequency of all state bouts except active sleep and decreased total sleep-wake transition and active and quiet sleep bout lengths. Hospital differences were found for total active waking, frequency of quiet waking and quiet sleep bouts, and the mean length of quiet waking and sleep-wake transition bouts. Mechanical ventilation and race also affected a couple variables.
Conclusion: Changes over age in state bout frequencies and lengths affected the development of sleep-wake states in preterm infants, but the nature of these relationships differed before and after term. These differences probably reflect both the infants underlying neurological status and the differing environments experienced by infants before and after term.

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Changes in Sleep Architecture and Respiratory Function Following Adenotonsillectomy in Children with Obstructive Sleep Apnea Syndrome

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Introduction: Adenotonsillectomy (T&A) remains the primary treatment for obstructive sleep apnea syndrome (OSAS) in children. Significant reductions in respiratory abnormalities and arousal index occur after T&A with no apparent changes in sleep structure. However, it remains unknown whether children after T&A normalize their sleep architecture or retain intrinsic differences in sleep structure. Thus, we assessed changes in sleep architecture in children following T&A, and compared their sleep characteristics after T&A to a control population.
Methods: Polysomnographic evaluation was performed before and after T&A in 70 children (66% male). In addition, 22 control children were studied.
Results: 70 children aged 1-17 years (mean: 6.6+/-4.3 years) were studied twice within 4.3+/-3.2 months. AHI improved from 25.6+/-34.6 to 9.3+/-1.1 after T&A, and these reductions in AHI occurred in 63/70 children, with worsening of AHI in 5 and no changes in 2 patients. However, 21 children had residual AHI <1 /hrTST, 32 children had post T&A AHI between 1 and 5/hrTST, and 17 children had residual OSA with AHI>5 /hrTST. For all children, total arousal index (TAI) and respiratory arousal index (RAI) were significantly improved, with reciprocal increases in spontaneous arousal index (SAI). In those with complete normalization of AHI, SWS percentage increased, while no changes in SWS occurred in the 2 other groups with residual respiratory disturbances. No changes in REM emerged for all 3 outcome groups after T&A. Compared to control children, those with normal post T&A respiratory patterns had higher SWS percentage with reciprocal reductions in stage 2 NREM sleep.
Conclusion: Our findings indicate that T&A yields substantial improvements in respiratory abnormalities in the vast majority of OSAS patients along with reciprocal changes in SAI and RAI distribution. However, complete normalization of respiratory variables occurs in only 30% of patients. For the latter, residual increases in SWS (expressed as percentage of TST) are apparent with no changes in REM sleep.

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Arousal Criteria in Snoring Children

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Introduction: In contrast to adult patients with sleep-disordered breathing (SDB), pediatric patients are less likely to develop arousals during respiratory events when such arousals are identified using the 3-sec rule. This has led to the assumption that children are more likely to preserve sleep homeostasis. However, despite the absence of obvious substantial "sleep fragmentation" in the polysomnographic record, children manifest behavioral symptoms suggestive of the presence of such morbidity. Thus, adult arousal coding criteria may be inadequate in children. The aim of this study was to examine whether different scoring criteria for arousal would improve differentiation between children with SDB, primary snoring, and control children.
Methods: Thirty overnight polysomnographic records corresponding to age- and gender-matched children with obstructive sleep apnea (OSA; n=10), 10 children with primary snoring (PS), and 10 control (CO) children were analyzed by blinded investigators using 3 different arousal scoring criteria: (1) ASDA scoring arousal, i.e., 3 sec rule; (2) ASDA modified criteria, i.e., >1.5 sec rule; (3) arousal was considered to be present for any visually recognizable shift in the EEG frequency.
Results: Independent of scoring criteria, OSA patients had more arousals than either PS or CO. However, using the 3-sec rule allowed for differentiation between PS and CO, while scoring of arousals using either 1.5 sec or EEG frequency shift criteria did not differentiate between PS and CO.
Conclusion: Although the use of ASDA arousal criteria has not been scientifically validated in children, the 3-second rule allows for optimal discrimination between OSA, PS, and control children. Until improved methods of arousal detection are specifically developed for children, 3-sec arousals should be used.

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Polysomnographic Measures And DSM-IV Behavior Disorders Before And After Adenotonsillectomy In Children

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Introduction: We previously showed that children scheduled to undergo adenotonsillectomy, frequently for a clinical diagnosis of obstructive sleep-disordered breathing (SDB), often have a DSM-IV-defined disruptive behavior disorder (DBD): either attention-deficit/hyperactivity disorder, conduct disorder, or oppositional/defiant disorder. In many operated children with DBDs, a psychiatric condition usually considered chronic can no longer be diagnosed one year after surgery. We therefore examined whether pre-operative polysomnographic measures of SDB severity predict amelioration of DBDs after surgery, and whether post-

operative measures explain persistence of DBDs in some children.
Methods: Twenty-five children, 40% male, with a mean age of 7.6 years (range 5-11), were included in this analysis. They participated in ongoing research on children scheduled for adenotonsillectomy for any clinical indication. Each child was found to have a DSM-IV diagnosis of a DBD, as determined by interviews with a board-certified child psychiatrist and corroborated by a validated structured interview, the Diagnostic Interview Schedule for Children. Behavioral assessments and nocturnal polysomnography were performed just before and one year after adenotonsillectomy. Polysomnograms were scored by one certified technician masked to subject name and operative status. Obstructive apneas and hypopneas were 2 breaths or longer in duration. Respiration was monitored by thermocouples and piezo-electric belts. Esophageal pressure monitoring, tolerated in 16 (64%) of the subjects, was used to define peak negative inspiratory pressures, percent of sleep time with esophageal pressure more negative than -10 cm of water, and rates of respiratory event-related arousals. Rates per hour of sleep of these latter events, plus apneas and hypopneas, defined the respiratory disturbance index. Other analyzed variables included arousal index, minimum oxygen saturation, maximum end-tidal CO2, percent of sleep time spent with end-tidal CO2 >50 mm Hg, and periodic leg movement index.
Results: Twenty-five children, 40% male, with a mean age of 7.6 years (range 5 - 11), were included in this analysis. They participated in ongoing research on children scheduled for adenotonsillectomy for any clinical indication. Each of the 25 children was determined to have a DSM-IV diagnosis of a DBD, as determined by interviews with a board-certified child psychiatrist and corroborated by results of a validated structured interview, the Diagnostic Interview Schedule for Children. Behavioral assessments and nocturnal polysomnography were performed just before and one year after adenotonsillectomy. Polysomnograms were scored by one certified technician masked to subject name and operative status. Obstructive apneas and hypopneas were 2 breaths or longer in duration. Airflow was monitored by thermocouples; chest and abdomen excursion by piezo-electric belts. Esophageal pressure monitoring, tolerated in 16 (64%) of the subjects, was used to define peak negative inspiratory pressures, percent of sleep time with esophageal pressure more negative than -10 cm of water, and rates of respiratory event-related arousals. Rates per hour of sleep of these latter events, plus apneas and hypopneas, defined the respiratory disturbance index. Other analyzed variables included arousal index, minimum oxygen saturation, maximum end-tidal CO2, percent of sleep time spent with end-tidal CO2 >50 mm Hg, and periodic leg movement index.
Conclusion: Resolution of DBDs in nearly half of the children one year after adenotonsillectomy, coupled with evidence of persistently high work of breathing in children whose DBDs did not resolve, supports the hypothesis that SDB causes or contributes to DBDs. However, the finding that pre-operative SDB measures and scoring criteria fail to predict which children will improve highlights the need for new, more effective and outcome-relevant polysomnographic measures.

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EEG Spectral Analysis of Sleep in Children with Gilles de la Tourette Syndrome

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Introduction: Several studies have found poor subjective and objective measures of sleep in children with Tourette Syndrome (TS). Recent PSG study showed an increased level of arousals (>15sec of the epoch), using standard ASDA criteria. Arousals scored with these rules may not be a sensitive method to document sleep instability, especially in children. We hypothesized that more subtle EEG changes during the night, in absence of arousal, would be a more sensitive evaluation of sleep instability in children with TS.
Methods: 9 children with TS aged 11.2 +/- 1.8 yrs. and 9 control subjects aged 10.7 +/- 2.2 yrs had 2 consecutive nights PSG studies. The second night was considered for sleep analysis.The EEG signals were subjected to standard sleep analysis on first four cycles of the night. A spectral analysis with a Fast Fourier Transform (FFT) was also done on the C3-A1 channel using a 4-sec Hanning window using the same period. The absolute power values (uV2/Hz) of eight EEG components known to be sensitive to sleep disturbance (delta (0.5-4Hz),theta (4.5-7.5 Hz), slow alpha (7.5-9 Hz), fast alpha (9.5-11 Hz), slow sigma (11.5-13Hz), fast sigma (11.5-13Hz), beta (15.5-35Hz) and total power (0.5-45 Hz) were computed during period free of PSG standard arousals or movement time. Mann-Whitney-U tests were performed between groups.
Results: Compared to controls, no significant differences in sleep macrostructure were found, TS patients, however, having more stage 2 of NREM sleep ($p=0.06$). TS children showed more arousals ($p<0.01$) throughout the night. The FFT analysis did not reveal any significant differences in all considered frequency bands but lower slow sigma power ($p<0.02$) was present in the last third cycle of the night.
Conclusion: Our preliminary results support the notion that sleeps instability more than sleep disruption is present in children with TS. Reduced sigma activity, which may reflect decreased sleep fusorial activity, could represent altered sleep stability process in these children.

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Leukotriene Modifier Therapy for Mild Sleep Disordered Breathing in Children

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Introduction: Adenotonsillectomy (T&A) is the most common and effective treatment for children with SDB. However, this approach is reserved for children whose AHI> 5 /hr TST. While an AHI<1 hr/TST does not need any intervention, there is no consensus on the appropriate management of symptomatic children with AHI >1 but <5 (mild SDB), since their morbidity is not severe enough to justify the risks of T&A. We have shown that leukotriene receptors are abundantly expressed in tonsils and adenoids of children with SDB. We hypothesized that long-term administration of a leukotriene receptor antagonist such as montelukast, may lead to progressive reductions in the overall volume of the adenotonsillar lymphoid tissue impinging upon the upper airway, and ameliorate polysomnographic abnormalities in children with mild SDB.
Methods: In a single center open label study, 20 consecutive children were enrolled, and met both inclusion criteria (>2 and <10 years of age with mild SDB) and exclusion criteria (absence of craniofacial, neuromuscular, syndromic or defined genetic abnormalities, previous use of montelukast, acute upper respiratory tract infection, or use of any corticosteroids or antibiotics within the past 3 weeks, and children who already had adenotonsillectomy in the past). Patients received montelukast sodium either as a 4 mg tablet if aged < 5 years or 5 mg if older, once a day at bedtime. Outcome measures included measurement of adenoid-nasopharyngeal airway ratio (A/P ratio) from a lateral neck X-ray obtained prior and 16 weeks after initiation of montelukast, and overnight polysomnograms (PSG) conducted at these time points.

Adherence to therapy was determined from refill use and a questionnaire.
Results: 10 boys and 10 girls aged 5.5+/-0.45 years, BMI of 19.3+/-0.87 kg/m2, were studied. The A/P ratio decreased from 0.71+/-0.03 before montelukast therapy to 0.49+/-0.02 ($p<0.0001$) at 16 weeks of treatment. AHI decreased from 3.01+/-0.23 to 2.31+/-0.39 ($p=0.06$), and although total arousal index (TAI) did not decrease significantly (18.44+/-1.57 to 15.88 +/-1.12 ,$p=0.19$), the respiratory arousal index (RAI) decreased significantly from 9.92+/-0.5 to 3.27+/-0.32 ($p<0.0001$) Similarly, a newly developed measure of sleep pressure in snoring children (SPS= (1-spontaneous arousal index/TAI)*(respiratory arousal index/TAI) was markedly improved after montelukast treamtment from 0.26+/-0.02 to 0.05+/-0.007 ($p<0.0001$). No adverse drug reactions were observed, compliance was satisfactory, and no attrition occurred.
Conclusion: A 16-week course of montelukast therapy is associated with significant clinical improvements in children with mild SDB, as evidenced by reductions in size of adenoid tissue and polysomnographic abnormalities. Large scale double blind placebo controlled studies will be needed to confirm these findings, and to determine the optimal duration and efficacy of this novel approach to pediatric SDB.

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Prevalence of Sleep Disorders among Urban Indian Seven-year-old Children

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Introduction: Sleep disorder breathing in children is being increasingly recognized as a cause of neurocognitive and cardiovascular morbidity. A recent study among middle age urban Indian men reported a prevalence rate of 7.5% for obstructive sleep apnea hypopnea syndrome. This high rate is believed to be due to the unique craniofacial features of this population. However, craniofacial risk factors for obstructive breathing in adults have been shown to be present from childhood. To our knowledge there is no prior report of prevalence of sleep disordered breathing in Indian children. The prevalence of obesity and allergic respiratory illness, both risk factors for sleep disordered breathing, is on the rise in urban India. The goal of this study was to estimate the prevalence of sleep disorders and obstructive breathing during sleep in Indian children living in an urban environment.
Methods: Participants were recruited from four schools in the city of Ludhiana, an urban industrial city in India. This study was approved by the administration of the respective schools and questionnaires were distributed to all First Grade students. Questions included history of sleeping environment, snoring, nocturnal awakening and daytime sleepiness. Of the 575 children sampled, 515 returned questionnaires (90.3%).
Results: The mean age of the 515 children in the cohort was 7.12 years (±0.25), 53.9% were boys and 46.1 % were girls. 354 children (68.7%) reported sleeping in the parent's room regularly, out of whom 186 (36%) also had a sibling sleeping in the parent's room. 139 children (26.9%) shared a room with sibling only and only 15 children (2.9%) slept alone. Snoring apart from that with colds was present in 15.5% of children. Children with snoring were more likely to have a parent who snored as compared to children who did not snore (62.7% Vs 30.2%, $p<0.05$). Nocturnal awakening, at least once every night, was reported in 25.9% of children and was not associated with history of snoring ($p>0.05$). Teeth grinding while asleep was present in 26.6% and talking during sleep in 16.4% of the children. Difficulty waking up in the morning was reported in 52 children and was associated with history of snoring apart from colds ($p=0.05$).
Conclusion: This is the first report of prevalence of sleep disorders in Indian children. Obstructive breathing during sleep, as reported by parents, was present in 15.5% of urban Indian seven-year-old children and was associated with history of snoring in parents. Regular co-sleeping is common in this culture and was not associated with an increased report of obstructive breathing during sleep or nocturnal awakening.

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Clinical Presentation of Sleep Disordered Breathing in 6–11 Year Old Children: The Tucson Children's Assessment of Sleep Apnea Study (TuCASA)

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Introduction: Sleep disordered breathing (SDB) in school children has been associated with habitual snoring (SN), excessive daytime sleepiness (EDS), learning and behavioral problems, and parasomnias. Most children with SDB present to their physician with SN, however, what other predictors might assist the clinician in deciding whether or not to refer the child for polysomnography? The clinical presentation of SDB has not been evaluated in a community sample of children using full polysomnography (PSG). The TuCASA study utilizes home PSG to determine the relationship between SDB in children and symptoms, physiologic/anatomic risk factors, and performance on neurobehavioral measures.
Methods: Parents of all children in 19 Tucson elementary schools were asked to complete a 13-item survey inquiring about sleep symptoms attributable to SDB. SN, EDS, witnessed apnea (WA), learning problems (LP), and insomnia (INSOM) were present if symptoms occurred 'frequently' or 'almost always'. Parents were also asked if their child was easily distracted, acted as if they had a 'motor running', or were fidgety 'frequently' or 'almost always'. Parents of children who met the study criteria were asked if their child would permit an overnight, unattended recording of their sleep. Polysomnograms were obtained with the Compumedics PS–2 system and were scored according to recently published criteria. On the night of the PSG, a Sleep Habits Questionnaire (SHQ) was completed by parents which asked questions pertaining to sleep habits, parasomnias, and daytime activity level. Enuresis (EN) and sleeptalking (ST) were present if they occurred more than 5 times per month. Sleep terrors (TR) were present if the child awoke at night afraid and crying. Sleepwalking (SW) was present if it occurred more than 3 times per month. The upper airway was viewed by the research technician on the night of the PSG and a subjective assessment of airway diameter was made on a scale of one (open) to three (narrow). Respiratory Disturbance Index (RDI) was defined as the number of apneas and hypopneas per hour of sleep with a 3% oxygen desaturation. Children were determined to have SDB if they had an RDI of 1 event per hour or greater.
Results: The survey response rate was 30.6%. Of the 480 subjects completing a PSG, 50% were males and 42.3% were Hispanic with a mean age of 8.3 years (range 6–11). The median RDI was .49 (range 0–29). In bivariate analyses, the following variables were significantly associated with SDB at $p<.05$: male gender ($p<.01$), SN ($p<.001$), EDS ($p<.007$), LP ($p<.004$), SW ($p<.02$), ST ($p<.006$). These variables were placed into a logistic regression with SDB as the dependent variable. SN and male gender were significantly predictive of SDB with odds ratios of 3.0 [$p<.001$, (1.75, 5.2)] and 1.8 [$p<.01$, (1.1, 2.8)] respectively.
Conclusion: In this population based sample of 6–11 year old school children, those with habitual snoring are 3 times more likely to have SDB than those who do not snore. Boys are 1.8 times more likely to have

SDB than girls. SDB is also associated with EDS, LP, SW and ST.

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Attention-Deficit /Hyperactivity Disorder With And Without Obstructive Sleep Apnea-Outcome Of Methylphenidate And Surgical Treatment

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Introduction: In recent studies, there has been some speculation about the relationship between Attention-Deficit/Hyperactivity Disorder(ADHD) like symptoms and sleep disorder, such as obstructive sleep apnea(OSA). This study intends to investigate of ADHD children with and without OSA and analyze of different treatment outcome.
Methods: 122 children 5 to 13-year-old(mean 8.2 years),diagnosed as ADHD based on DSM-IV criteria and completed the Test of Variable Attention-Visual(TOVA-V), Child Behavior Checklist(CBCL). Pediatric Sleep Questionnaire(PSQ) and polysomnography(PSG). Based on PSG results parents were offered following choice:(1)adenotonsillectomy(T and A)(2)methylphenidate(3)no treatment.
Results: 79 children were diagnosed with ADHD and OSA(AHI>1), and 43 as ADHD without OSA. In the ADHD with OSA group, the treatment subdivided in T and A=27;methylphenidate=36;no treatment=16. Versus ADHD without OSA group were subdivided in methylphenidate=28;and no treatment=18. Both groups(T A and methylphenidate in ADHD with OSA group)improved on omission,commission,ADHD score of TOVA,CBCL,without significance between group. But the response time and response time variability of TOVA were significantly better improved in T A group(using ANOVA). ADHD with OSA and without OSA group using methylphenidate treatment,there was no significant difference in degree of change on TOVA,CBCL(using MANOVA).
Conclusion: ADHD with OSA treated with T and A had better improvement in response time and response time variability of TOVA. There was no other significant difference between these groups.

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Prolongation Of QT Intervals In Victims Of Sudden Infant Death Syndrome: A Polysomnographic Study

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Introduction: Recent data suggested that prolonged QTc intervals are associated with Sudden Infant death Syndrome (SIDS). We hypothesized that QTc intervals in future SIDS victims were longer than those of healthy control infants.
Methods: QTc intervals were measured in the sleep recordings of 18 infants who eventually died of SIDS and 18 control infants. The infants of the two groups were matched for sex, gestational age, postnatal age, weight at birth and sleep position during recording.
Results: Compared to the control infants, the future SIDS victims were characterized by longer QTc intervals during the night during total sleep (p=.019), REM (p=.045) and NREM sleep (p=.029). Two out of 18 future SIDS victims but no control infants had QTc intervals > 440 ms. Dividing the night in three equal parts, this difference was always present, but most marked during the first part of the night (p=.030), especially in REM sleep (p=.041). There was a negative correlation between parasympathetic tonus and the maximum duration of QTc intervals (r=-0.35, p=.049) in NREM sleep.
Conclusion: Based on the present findings, it can be postulated that QTc intervals were increased in some future SIDS victims. This difference could be related to the autonomic dysfunction already reported in these patients.

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Neonatal State Prediction and Maturation Using Dimensional Analysis

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Introduction: Traditional linear methods of signal analysis rely primarily on the frequency characteristics of the signal, often neglecting the temporal characteristics that are also encoded in the signal. Nonlinear signal analysis methods make use of this additional information by viewing physiologic behaviors as a measurement of the state of some dynamical system. Using such measurements, the time evolution or dynamics of the EEG system for example, can be reconstructed in multi-dimensional phase space. This reconstruction can then be used to reveal dynamical properties of the system not apparent from classical frequency analysis.
Methods: Dimensional analysis (DA) was selected to measure the complexity of a biologic system (i.e. EEG) based on the geometrical properties of the system's evolution in the phase space. DA has been used to study a variety of neurological states including anesthetic coma, epilepsy, and states of arousal including sleep. Our current research applied DA to neonatal sleep states at increasing gestational ages up to fullterm age. A total of 116 overnight EEG/polygraphic recordings were performed on 55 neonatal subjects between the gestational ages of 28 to 43 weeks; thirty-one of the infants were less than 33 weeks gestational age. The remaining subgroup were fullterm (i.e. > 37 weeks gestation). Fourteen channels of EEG and polygraphic channels that included EMG, EOG, ECG, nasal, thoracic and abdominal respirations and blood oxygen saturation were utilized. State assignments were initially assigned by visual analyses. A single EEG channel (FP1-C3) was selected for dimensional analysis. Two-tailed T tests were used to test for differences in DA between active and quiet sleep, preterm and fullterm neonates, and as a function of maturation.
Results: 1- A significant difference between active and quiet sleep ($P < 0.001$) was noted for the fullterm infant. 2- A strong significant positive correlation between DA and conceptional age was noted ($P < .001$). 3- DA for both active and quiet sleep increased in complexity as the baby matured towards fullterm age. 4- Lower dimensionality (i.e. less complexity) was noted for a healthy preterm cohort at corrected fullterm age, compared to the fullterm subgroup.
Conclusion: Dimensional analysis demonstrated a strong positive correlation for both active and quiet sleep as the infant matured to corrected term ages. Lower dimensionality (i.e. less complexity) was noted for the healthy preterm cohort at corrected fullterm age, supporting the concept of physiologic dysmaturity as a reflection of neuroplasticity in the preterm cohort as compared to the fullterm group. Future studies will investigate dimensional analysis for larger neonatal cohorts at successively older gestational ages in the context of medical illness, to detect deviations from expected maturational trends.

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Restless Legs Syndrome in Children

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Introduction: Restless Legs Syndrome is a recognized and well-described disorder in adults, yet recent evidence shows its onset in childhood as well. Few publications have described Restless Legs Syndrome in children, mostly in patients with ADHD. We present our case series of 10 children with Restless Legs Syndrome, 40% of them without a concomitant ADHD.
Methods: We have retrospectively reviewed the charts of 207 children who presented with sleep disorders at the Sleep Center of the Cleveland Clinic Foundation, between 2000 and 2003. These children were referred to the Sleep Center for evaluation of a variety of sleep disorders. Following a thorough neurological and general examination, and a comprehensive sleep history, theses children underwent a full-night in-lab polysomnographic evaluation with monitoring EEG, EOG, EMG (chin and leg), EKG, thoracic and abdominal belts, pulse oximetry, oronasal airflow, the end tidal CO2, and video monitoring. The diagnosis of Restless Legs Syndrome was established based on two major criteria: a) polysomnographic: by demonstrating periodic leg movements during wakefulness and sleep, and b) clinically: by symptomatic description of creepy, crawly, achy, or difficult to describe uncomfortable sensation, which is deep in the legs, unilateral or bilateral, worse at rest or inactivity, with partial or total relief by movements, and worse in the evening and night.
Results: Out of the 207 children who were seen in the sleep center since the year 2000, ten patients were diagnosed with Restless Legs Syndrome (incidence rate is 5%). The mean age was 8 (+/- 6) year old, only 30% were females, 70% had insomnia, 80% had an excessive daytime sleepiness, 10% had iron deficiency anemia, 60% had a progressive course, 40% had family history of RLS, and only 60% had ADHD. Different treatment modalities were used, including education of sleep hygiene, Gabapentin, Clonidine, and Ropinirole. Treatment was commenced in 90% of patients (one patient did not show up after completion of his work up), 80% of compliant patients showed different degrees of symptomatic relief, yet the compliance rate with treatment and follow up was only 50%.
Conclusion: This data supports that Restless Legs Syndrome does occur in children even in the absence of ADHD. Clinicians should be aware that Restless Legs Syndrome can occur in childhood and may be more common than it was previously thought. More studies are needed to further characterize Restless Legs Syndrome in Children.

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Autonomic Dysfunction During Sleep In Familial Dysautonomia Assessed By Heart Rate Variability Analysis

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Introduction: Familial Dysautonomia (FD) is a rare autosomal recessive disorder involving multiple systems: Autonomic Nervous System (ANS), cardiovascular, respiratory, gastrointestinal, musculo-skeletal. Early diagnosis and aggressive treatment improves survival rate, however sleep death and sudden death remain the most frequent final events. Previous studies demonstrated a wide range of sleep related breathing (SRB) abnormalities in most patients, however no appropriate treatment guidelines exist. This study aimed to estimate the occurrence and severity of cardio-autonomic dysfunction during night-time sleep in order to use this variable as an additional indicator of the vulnerability of FD patients.
Methods: The study included 11 FD patients (age 25.3, range 18-42, 9 female). All completed a sleep questionnaire (including information on time in bed, difficulty falling asleep and waking up, awakenings, nocturnal cough, body and limb movements, snoring, daytime napping and excessive daytime sleepiness (EDS)). All subjects underwent autonomic sympathetic challenge (change of position from supine to standing), 24 hour Holter recording, and actigraphy for seven consecutive days. Quantitative assessment of ANS function was performed by time-frequency spectral analysis of heart rate variability (HRV) derived from the Holter recordings. The obtained parameters are known to reflect sympathetic and parasympathetic activity (VLF and LF), mainly parasympathetic activity (HF), and the autonomic balance (LF/HF). Blood pressure and heart rate were measured during autonomic challenge. Results for bedtime HRV in FD were compared to those obtained from healthy, sex and age matched controls that underwent polysomnography.
Results: The autonomic challenge caused a steep decrease in blood pressure, uncompensated for by any changes in heart rate, sympathetic or parasympathetic activity. No subjective dizziness or pre-syncope were reported. FD patients reported time to bed between 22-01, sleep-time of 7+2 hours, 70% reported 1-2 hours regular napping, 10% difficulty falling asleep, 45% nocturnal cough, 45% increased movement during sleep, 18% limb jerks, 27% snoring, 36% EDS. Actigraphy revealed sleep fragmentation and decreased sleep efficiency in all patients. Surprisingly, mean HR in FD was similar during daytime and night sleep. HRV was low in FD: Total power, LF and HF power were significantly reduced in FD compared to normal controls (t test, $p<0.03$), while the differences in power density in the VLF range did not reach significance. There was no significant difference between groups in the percentage of sleep time spent in a state of sympathetic predominance (23.9%+ 3.7% and 22.4%+8.6%). Sleep HR was significantly higher in FD patients than in normal controls (t test, $p<0.03$) during both periods of sympathetic and of parasympathetic predominance. Three patients had asystoles of 10-15 seconds during sleep.
Conclusion: Actigraphy revealed a more disturbed sleep than suggested by self reports made by patients. Patients have severely abnormal autonomic regulation with no compensatory changes needed to sustain normal homeostasis during wakefulness and during sleep and may not react appropriately to respiratory pauses during sleep. This lack of compensation represents the most likely cause of the increased susceptibility of FD patients to sleep/sudden death. Periodic sleep studies in FD patients may indicate the need of initiation of adequate respiratory support that can improve both quality of life and survival.

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Physiologic Brain Dysmaturity and Neurodevelopmental Outcome

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Introduction: Specific physiologic measures during sleep have been used as surrogate markers of brain remodeling, termed the physiologic dysmaturity index. This index represents adjustments that the developing brain makes in functional organization at successively older post-conceptional ages to stresses of environment or medical illness. Dysmaturity may also represent altered brain development with greater risks for suboptimal neurodevelopment.

Methods: Seven EEG-sleep measures were determined by a statistical selection process to represent differences in sleep behavior between preterm and fullterm neonatal cohorts. A mathematical calculation was used to estimate the distance from the mean of a control group (i.e. fullterm) for each of these physiologic measures, and then the Mahalanobis Distance (MD) was used to calculate the index for each preterm and fullterm subject. MD differs from conventional Euclidean distances because it takes into account correlations computed on the basis of these seven EEG-sleep dimensions. There is a one to one relationship between the MD of a point from the mean and the probability of observing that value given that the data follows a multivariate normal distribution. By using the MD calculation we can preserve accelerated or delayed expressions of particular sleep behaviors for healthy neonatal cohorts that differ based only on prematurity. Each of the seven measures suggested altered physiologic expression of sleep behaviors; the preterm cohort expressed lower spectral beta EEG energies, higher spectral EEG correlations, higher sleep percentages, longer sleep cycle lengths, fewer arousals, less REMs, and lower respiratory regularity. We are investigating sleep ontogeny and neurodevelopmental outcome for 153 healthy neonates without postnatal illnesses (63 fullterm and 93 preterm) compared with 201 medically high-risk neonates (106 fullterm and 95 preterm). MD was calculated for all neonates based on one of serial multi-hour EEG-sleep studies obtained between 35 and 43 weeks corrected age. Neurodevelopmental assessments at 9, 18 and 27 months were performed using Bayley Developmental Scales that were compared with components of this dysmaturity index. Two-tailed T-test calculations were performed, comparing the healthy group to the medically at risk group with respect to an MD calculation, individual values of the seven dysmaturity index components that comprise the MD and Bayley Scores at three successively older ages.
Results: 1- MD was significantly different in the healthy group compared to the medically at risk group ($p < 0.0001$). 2- Five of the seven dysmaturity components - spectral correlation, spectral beta, arousal index, REM index and respiratory ratio were significantly different ($p < .05$) between the healthy and the medically at risk group between 35 and 43 weeks corrected age. 3- Significant correlations were noted between the Bayley Scores and the combined cohorts of healthy and medically at risk groups with respect to REM index, arousal index, and respiratory regularity at 9, 18 or 27 months.
Conclusion: Automated neurophysiologic methodologies can assess for altered neonatal state organization and maturation, and offer an opportunity to create a surrogate marker of activity-dependent brain development in a high-risk neonatal population that predicts compromised neurodevelopmental outcome.

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Racial Differences in Reported Napping and Nighttime Sleep in 2- to 8-Year-Old Children

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Introduction: Existing reports on developmental sleep patterns have indicated that children most often stop napping and consolidate their sleep into one nocturnal period between ages four and five years (Weissbluth, 1995; Iglowstein et al., 2003). There is evidence, however, that a consolidated sleep pattern may occur later during development in Black than White children (Lavigne et al., 1999). The purpose of the present study was to examine racial differences in reported napping and nighttime sleep of 2- to 8-year-old children and to identify factors that may account for these differences.
Methods: Data were collected on 1043 children (73.5% White-non Hispanic; 50.4% male) aged 2- to 8-years from southern Mississippi, USA. Demographic characteristics of the sample were comparable to 2000 census data for the same region. There was a proportionate distribution of Black and White children across age groups. Caretakers reported their child's typical weekday and weekend bedtime and rise time, the number days/week their child napped, and typical nap duration. Two hundred fifty-four caretakers of 3- to 5-year-old children also completed the Behavior Assessment Scale for Children (BASC).
Results: Six main findings emerged from data analysis. (1) Black children displayed a more gradual decline in napping as they matured. At ages 5 through 8, a statistically larger proportion of Black children were reported to be napping (all ps < .001). At age 8, 39.1% of Black children napped, compared to only 4.9% of White children. Black children napped significantly more days per week than White children ($F_{age}=17.3$, $p<.001$; $F_{race}=7.2$, $p<.001$). (2) Black children had significantly less nocturnal time in bed compared to White children ($F_{age}=6.2$, $p<.001$; $F_{race}=23.5$, $p<.001$). (3) Black but not White children slept significantly less on weeknights than on weekends ($F_{timexrace}=7.59$, $p=.006$). (4) Despite differences in sleep distribution, weekly total time in bed (diurnal and nocturnal sleep) was nearly identical for the two racial groups across each year of age. (5) Multiple regression analysis revealed that demographic variables, such as SES and single mother status, were related to, but did not fully explain napping differences. (6) Napping in preschoolers was not significantly related to any of the BASC internalizing or externalizing domains.
Conclusion: While total time in bed is similar in Black and White children, there are remarkable differences in reported napping and nighttime sleep patterns beginning as early as three and extending to at least eight years of age. Cultural factors are likely to be importantly related to these differences, but biological factors may also be involved. These differences in children highlight the need for normative data delineated by racial groups. Understanding racial differences may also lead to greater understanding of factors underlying sleep-wake regulation.

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Genioglossal EMG Activity in Children with Sleep Apnea versus Controls during NREM and REM Sleep plus Obstructed Breathing Events

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Introduction: The determinants of upper airway patency include static pharyngeal mechanics, neuromuscular activity, and luminal pressure. Children with the obstructive sleep apnea syndrome (OSAS) have narrower and more collapsible airways compared to normal subjects. There is, however, considerable overlap in measures of airway size between children with and without OSAS, suggesting a role for neuromuscular compensation. The prominent role for active neuromuscular mechanisms is further evidenced by the ability of patients with OSAS to sustain stable breathing during at least a portion of sleep, the lack of obstruction during wakefulness and stage 4 sleep, the REM predominance of apnea, and the tendency for sedatives to induce apnea. The neuromuscular compensatory mechanisms active in maintaining airway patency during sleep in children are not well understood. Our objectives were a) To determine the sleep state effect on the amplitude and variability of the EMGgg; and b) To evaluate the EMGgg during apniec breaths compared to stable sleep (non-apniec/non-arousal) and wakefulness.
Methods: Using a custom intra-oral surface electrode to record pharyngeal dilator muscle activity (the genioglossus (EMGgg) normalized to

the wakeful baseline), we performed overnight polysomnograms in three groups of children 1) 8 controls; 2) 4 with OSAS on CPAP; 3) 5 with OSAS without CPAP.
Results: In normal subjects, the EMGgg for stable breaths during wakefulness, stage 2, stage 4, and REM was 100 ± 5, 66 ± 4*, 59 ± 3*, and 50 ± 8%*, respectively (*p < 0.05 for the amplitude, compared to wakefulness). In OSAS patients on CPAP, the EMGgg for stable breaths during wakefulness, stage 2, stage 4, and REM was 100 ± 7, 76 ± 12*, 72 ± 5*, and 68 ± 19%*†, respectively (*p < 0.05 for the amplitude, †p < 0.05 for the variability, compared to wakefulness). In OSAS patients without CPAP during stage 2, the EMGgg for apniec breaths (41 ± 6%) was lower than stable breathing (96 ± 6%)(p < 0.05) and wakefulness (100 ± 11%)(p < 0.05). In OSAS patients without CPAP during REM, the EMGgg for apniec breaths (28 ± 7%) was lower than stable breathing (81 ± 9%)(p < 0.05) and wakefulness (100 ± 11%)(p < 0.05).
Conclusion: These data confirm that 1) REM sleep, and to a lesser extent stage 2, is associated with lower, more variable EMGgg than during wakefulness. 2) Oscillations in EMGgg may account for the temporal occurrence of sleep apnea during stage 2 and REM in anatomically predisposed children.

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Normative Vigilance Performance of Children on the PVT: Data from the Tucson Assessment of Sleep Apnea Study (TuCASA)
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Introduction: Psychomotor vigilance has been widely used adult research to measure attentional control and sleepiness. It has applied utility in the prediction of functional abilities such as driving. The wide spread use and portability of the Psychomotor Vigilance Test (PVT) makes it attractive for use with children in applied and research settings. However, there currently is no available normative data against which to judge the performance of children on the PVT. Generalization or downward application of adult normative data is not valid. The present study provides some normative values for children on this vigilance test and relationships with RDI, parent reported sleepiness, and age.
Methods: A prospective cohort study of 503 children from public schools each underwent unattended in-home overnight polysomnography as part of the TuCASA study. The majority of those parents (389) also agreed to neurocognitive testing for their child which took place within a research setting approximately one month after each sleep study. An unmodified PVT task was administered to children ages 6-11. The PVT was administered last in the 1.5 hour battery of tests. The test environment included bathroom breaks, adequate lighting, and no distractions. Time of day for testing varied widely and was not included in the present study. Exclusion criteria included those children on medication for ADHD or those with a diagnosis of ADHD. Because of skewness the RT and RDI variables were transformed for all analyses.
Results: Average age of children was 8.85 (SD 1.6). The raw Mean RT for all children was 546.12 msec (SD 264.0) and the Median was 414.46. The RT distribution was positively skewed and thus the transformed RT was used in subsequent analyses. The average fastest 10% of RTs was 275.7 and the average slowest 10% of RTs was 1536.6. The average number of lapses was 26.7. No PVT indices were linearly related to log-transformed RDI in the general sample as indicated by non-significant bivariate correlations. PVT means between the upper quartile of the RDI distribution and lower part of the distribution were not significantly different. The PVT was not linearly related to parents perception of their childs attention or sleepiness during the day or the evening. Performance on the PVT was related to age. Each year of age was associated with a positive improvement in performance. Bivariate correlation between Mean RT and age was .69. Significant unstandardized linear regression coefficients with age were obtained for MeanRT (-.25, p=.000), lapses (-8.16, p=.000), and the intercept (.24, p=.000). Within-subject change during the task, indicated by slope, did not significantly change with age.
Conclusion: Age-related performance changes were found with average RT as well as some types of errors. Although overall RT improved with age, ability to sustain attention over time on this task may not improve significantly between the ages of 6 and 11. Test-specific sensitivity to development of attention needs to be explored more fully with the PVT.

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Association between Sleep Disordered Breathing and Oral Malocclusion in Childhood: Preliminary Data
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Introduction: Recent epidemiological studies have documented that the prevalence of malocclusion (MOC) in childhood is 50% to 70%. There are also evidences that the use of oral devices in subjects with MOC, improves polysomnographyc values of patients with obstructive sleep apnea syndrome (OSAS), suggesting that MOCs might play a role in the pathogenesis sleep disordered breathing (SBD). The aims of our study were to investigate the prevalence of MOC and the relationship between SBD and MOC in a cohort of pre-school- and school-aged children.
Methods: Five hundred non-selected children aged 3-11 years (median age 6.8 years) from Turi, a small town in the South part of Italy, were enrolled. The parents were asked to fill-out a questionnaire that sought informations about the clinical history of the children, nocturnal sleep disorders and the presence of evident defects of the oral cavity structures. Children were classified as habitual snorers (HS), occasional snorers (OS) and non-snorers (NS), using a 5 point evaluation scale (from 5: children always snored, to 1: children never snored during sleep or only when suffering for upper airways infections). All partecipants underwent an ortognatodontic examination. The dentist identified and classified MOCs in 3 classes, as recommended by Angle. Children defined as HS underwent nigh-time home sleep study. Subjects who had an Oxigen Desaturation Index (ODI) greater than 2 during the sleep study, underwent nocturnal polysomnographic monitoring (NPM) in our laboratory. Thus, we could make diagnosis of OSAS [Apnea/Hypopnea Index (AHI) >3] or of primary snoring (AHI < 1).
Results: Out of 500 questionnaire, 438 (87.6%) were returned, while 396 (79.2%) children performed the dentist examination. We obtained information from both, parents and the dentist, for a total of 382 (76.4%) children. Eighteen children (4.1%) were defined as HS, 140 (32%) OS and 276 (63%) were NS. The analysis of data about oral anomalies showed that 237 (62.0%) out of 382 children had MOC. We also observed a significant trend of distribution of MOC by age [(3 to 5 years) 48.5% vs (6 to 9 years) 68.6% vs (>10 years) 71.7%, respectively; p<0.0001]. Seven out of 16 HS underwent NPM and 2 of them had OSAS, 4 had primary snoring and one child did not have any SDB. The prevalence of MOC in children with OSAS was 100%; in fact, both children with OSAS, had associated MOC. Three out of 4 children with primary snoring had also MOC (75%). Among 9 children HS who did not showed SBD when monitored with the NPM, the prevalence of MOC was 66.7%. However, this trend was not statistically significant (100%

vs 75% vs 66.7%; p= 0.18).
Conclusion: Our study shows that the prevalence of MOC in our population is similar to that reported in literature. Although in our analysis the number of children with diagnosed SBD is small, we conclude that MOC is frequently associated with SBD in childhood.

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The Impact of Sleep Disordered Breathing on Cardiac and Motor Activity during Sleep in Children

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Introduction: Sleep Disordered Breathing (SDB) in children is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns. Recently SDB has emerged as a significant health problem expecially between age 3 and 6 with a prevalence up to 13% (Castronovo et al., J Ped 2003). Cardiac variability as well as motor activity during sleep in children with SDB have not being exensively studied as in adults. Carrol et al (Chest 1995) showed that SDB children had an increased number of body movements per hour respect to aged-matched controls. This can lead to an increased sleep fragmentation in these children. Aim of the present study was to assess heart rate variability and changes in body position in consecutive children referred for suspected SDB.
Methods: 783 children (470 M, 313 F) with a mean age of 4.9±2.2 (range 1-14) during a 3-year period (1998-2000) were included in the study. Children with chronic respiratory, cardiac or neuromuscular diseases were excluded from the study as well as children assuming steroids or benzodiazepines. All children underwent a clinical evaluation, a questionnaire including information on sleep-wake habits and one-night ambulatory cardio-respiratory monitoring. All recordings were analysed using a combination of visual and automatic analysis. The following parameters were calculated and analysed: ODI (number or oxygen desaturation >4%/hour), % of snoring time, HRVI (heart rate variation index), HR (mean heart rate), Min. SaO2 %, Mean SaO2%, MI (mobility index=number of body movements per hours) and BM (total number of body movements during sleep).
Results: On the basis of our experience with the device used, we considered pathological snoring when the percentage of time spent snoring was ≥ 15%. Children were classyfied into three groups according to respiratory results. Healthy (H) (n=439), habitual snorers (HS) (n=105) when snoring time was ≥ 15% and ODI < 5, obstructive sleep apnea (OSA) (n=239) when snoring time was < 15% and ODI ≥ 5. Respiratory results in H, HS and OSA groups were the following (mean ± SD): snoring time (%) 3.5±3.4, 39.1±24.8, 21.4±21.3 (H vs HS and OSA: p<.001); ODI 1.7±1.1, 2.1±1.1, 13.1±10.4 (OSA vs HS and H: p<.001); Min SaO2 (%) 89.3±5.2, 89.0±3.6, 82.2±7.9 (OSA vs HS and H: p<.001); Mean SaO2 (%) 92.7±1.2, 92.4±1.6, 90.9?2.3 (OSA vs HS and H: p<.001). HR and HRVI resulted significantly (p<.001) increased in OSA (HR = 96.7 ± 69.3; HRVI = 16.6 ± 11.4) respect both to HS (HR = 86.7 ± 9.1; HRVI = 14.1 ± 10.8) and to H (HR = 85.5 ± 11.4; HRVI = 14.7 ± 11.8). Habitual snoring resulted significantly related to increased heart rate. Motor results showed increased values in OSA (MI = 7.2 ±5.3; BM = 65.2 ±45.2) and HS (MI = 7.0 ±3.2; BM = 64.6 ±31.4) respect to H (MI = 5.6 ±3.7; BM = 54.6 ±29.8).In order to investigate the possible effect of age children were further stratified into three age categories: A (between 0-3 yrs), B (4-6 yrs) and C (> 6 yrs). There was a decrease of mean HR and of MI with increasing age while HRVI increases with increasing age .
Conclusion: OSA children showed a significant increase in cardiac variability during sleep while snoring alone did not have a significant impact on cardiac autonomic function. Both OSA and HS children had an increased sleep-related mobility compared to age-matched controls. This may explain the presence of diurnal conequences in terms of irritability and cognitive impairment also in children with snoring alone.

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Attention Deficit Hyperactivity Disorder in Children with Sleep Disordered Breathing

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Introduction: The Attention Deficit Hyperactivity Disorder (ADHD) is 'a persistent situation of inattention and hyperactivity/impulsiveness more frequent and serious than usually observed in children of equal level of development' (DSM-IV). ADHD symptoms might be affected by respiratory sleep disorders. Authors have documented that sleep disruption together with intermittent hypoxia and hypercapnia might alter the effectiveness of the restorative features during sleep and induce cellular and chemical stresses. This may interfere with functional omeostasis systems and cause neuronal and glial alterations in cerebral regions. The aim of our study was to evaluate the association of ADHD with different degrees of sleep disordered breathing (SDB) in a sample of preschool-aged and school-aged children.
Methods: Between March 2002 and June 2003, 84 children aged 3-13 years, who suffered for SDB, were enrolled. All children performed a nocturnal polysomnographic monitoring (NPM) in the sleep laboratory of our Pediatric Clinic at the University of Bari. Thus, we could make diagnosis of Obstructive sleep apnea syndrome (OSAS) [Apnea/Hypoapnea Index (AHI) >3] or primary snoring (AHI <1). Moreover, parents were asked to fill-out a form with questions that sought informations about the presence in their children of 18 specific symptoms of ADHD, according to the reccomendations of the DSM-IV. In this study, an index of the Inattention/Hyperactivity Scale (IHS) greater that 1.25, corresponding to 12 or more positive answers out of 18 on the questionnaire, was defined the predictive value for ADHD. The DSM-IV reports that when 6 out of 9 chronic symptoms related to inattention are associated to other 6 out of 9 symptoms of hyperactivity/impulsiveness it is possible to make diagnosis of ADHD combined type.
Results: The analysis of the questionnaires showed that 10 children (11.9%) had an IHS index greater than 1.25. The prevalence of hyperactive and inattentive behaviour (IHS>1.25) in patients with SDB is significantly higher than that of the general population (11.9% vs 3.9%; p <0.01; O.R. 3.3). Furthermore, we found a significant association between OSAS and hyperactive and inattentive behaviour (IHS>1.25) compared to the general population (16.6%vs 6.9%; p <0.005; O.R. 4.9); while among children with primary snoring we did not find such as significant relationship (7.1% vs 3.9%; p = NS; O.R. 1.9).
Conclusion: This study shows that it is important to investigate in children with SDB and attention deficit and/or hyperactivity-impulsiveness the presence of associated ADHD.

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Association Between Emotional Disorders and Sleep Disorders in Brazilian Elementary School Children

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Introduction: About 35% to 45% of school-aged children have Sleep Disorders. Features of emotional and behavior disorders are found in the Sleep Disorders (SD) children, but there are few researchs on specific emotional problems that could be associated with the sleep disorders. Some children can be adapted to their problems, or some emotional features can be inherent to the process of the child development. However when sleep disorders join those alredy existing emotional problems, we can lose the referencial that is producity emotions like anxiety, aggressiveness, impulsiveness and inhibition, and as well mood and attention. Many studies have presented Sleep Breating Disoders (SBD) in children associated with anxiety behaviors (AN) and aggressiveness (AG) however we do not find anything related to impulsiveneness (IM) and inhibition (IN). The goal of this study is to verify behaviors AN, AG, IM, and IN in children of public school with sleep disorders.
Methods: The sleep of 835 children (8 to 10 years old), of public schools of Sao Paulo City, SP, Brazil, had been evaluated with a sleep questionnaire, adapted of Bruni et al.. The children had been divided in 3 groups: general sleep disorders (GSD), sleep breating disorders (SBD) and without sleep disorders, control group (CG). The GSD was formed by children who had presented disorders of the arousal, disorders of excessive somnolence, disorders of initiating and maintainig of sleep and sleep awake transition disorders. General emotional disorders (GED) had been evaluated with Gestalt Bender Test, and included features of IN, IM, AN,and AG. The data was analyzed according to frequency of GED, AN, AG,IM, and IN comparing the GSD and SBD groups with the CG.
Results: The ratio of the General Emotion Disorders was similar among the groups General Sleep Disorders (98%), Sleep Breathing Disorders (97%) and Control Group (95%). The children with General Sleep Disorders presented more Anxiety (100%), more Impulsiveness (89%), and more Inhibition (48%) than those of the Control Group (59%, 78% and 41%, respectively), p<0,05. There is no difference regarding Inhibition, Impulsiveness, Aggressiveness and Anxiety comparing boys of Sleep Breathing Disorders and Control Group groups. The General Sleep Disorders boys presented more Impulsiveness (91%) and Inhibition (58%) than those of the Control Group (77% and 44%, respectively, p<0,05). The Sleep Breathing Disorders boys presented more Anxiety (95%) than the Control Group (75%), p<0,05. The General Sleep Disorders girls presented more Impulsiveness (88%) than those of the Control Group (80%), p<0,05. There was no difference for Impulsiveness, Inhibition, Aggressiveness, and Anxiety comparing girls of Sleep Breathing Disorders and Control Group.
Conclusion: The General Sleep Disorders children presented more Anxiety, Impulsiveness, and Inhibition comparing to the Control Group and the General Sleep Disorders boys presented Impulsiveness and Inhibition, while the General Sleep Disorders girls presented Impulsiveness. In the Sleep Breathing Disorders group the boys presented more Anxiety than the Control Group. As we suspect sleep disorders also determine many specific emotional disorders that need to be recognized by caregivers and teachers aiming treatment and general orientation

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Sleep Patterns in Adolescents with Chronic Musculoskeletal Pain

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Introduction: This study is a preliminary examination of sleep patterns in adolescents with chronic musculoskeletal pain syndromes (e.g., complex regional pain syndrome, fibromyalgia). A significant number of adolescents with chronic pain complain of sleep difficulties, with pain interfering with both sleep onset and sleep maintenance.
Methods: 29 adolescents who presented consecutively to a multi-disciplinary outpatient pain clinic participated in this study. Participants were 90% female and 86% Caucasian. Mean age was 15.4 years (range 12-17). Participants completed questionnaires during their clinic visit, including the Sleep Habits Survey, Reynolds Adolescent Depression Scale - 2nd Edition, Stait-Trait Anxiety Inventory - Trait Form, Pain Catastrophizing Scale and Functional Disability Inventory. During the subsequent two weeks, participants completed three 24-hour recall interviews asking about their sleep over the past day/night.
Results: Compared to a normative population of healthy adolescents (Wolfson et al., 2003), participants reported similar total sleep time for both school nights (approximately 7.2 hours) and weekend nights (approximately 9.0 hours), with both the pain and comparison groups reporting similar bedtimes (approximately 10:45pm weekdays, 12:30am weekends) and wake times (approximately 6:25am weekdays, 9:50am weekends). No significant relationship was found between amount of sleep and the following variables: depression, anxiety, catastrophizing, functional disability, or clinic pain ratings. Numeric pain ratings at bedtime and wake time significantly improved for 30% of participants after sleep (based on Farrar, et al. 2001 guidelines). In addition, greater total sleep times were found for adolescents reporting significant positive changes in pain ratings from bedtime to wake time (7.6 hours vs. 6.5 hours weekday, 9.3 hours vs. 7.9 hours weekend). Although these differences were not statistically significant [$F(1,22) = 2.5$ weekday, $F(1,25) = 2.2$ weekend], this may be due to a lack of power. Effect size calculations using Cohen's d indicate moderate effect sizes for both weekday (d=0.64) and weekend (d=0.67) differences. Finally, significant differences were found in terms of actual 24-hour data versus questionnaire reported night wakings ($\chi 2\ (4) = 14.1$, $p < .01$), with 59% of adolescents reporting two or more night wakings in their clinic intake questionnaire compared to only 26% of adolescents actually waking an average of two or more times.
Conclusion: Despite the frequent complaints about sleep heard among adolescent patients in the pain management clinic, this study found little difference between these adolescents and normative data. One hypothesis accounting for the subjective reports of poor sleep is that adolescents with chronic pain may be more sensitive to the sleep deprivation that is common in this age group, resulting in increased perception of poor sleep. Another possibility is misperception of sleep state in these patients. Furthermore, in terms of sleep disruptions, adolescents may be over-reporting this problem in clinic, as evidenced by the difference between clinic questionnaire and 24-hour recall interview reports of night wakings. Interestingly, pain ratings significantly decreased for adolescents who get more sleep at night as seen by changes in pain ratings. Clearly, additional research needs to be conducted to further investigate (1) sleep patterns in adolescents with chronic pain, utilizing additional measures such as actigraphy and/or polysomnography, and (2) the restorative function that sleep has on chronic musculoskeletal pain.

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Sleep In Children Following Discharge From The PICU: A Secondary Analysis Of The COPE Study

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Introduction: Children have significant sleep disturbances after discharge from the Pediatric Intensive Care Unit (PICU). These disturbances may be decreasing because of shortened length of stay. We evaluated the frequency of sleep disturba

Methods: We performed a secondary analysis for sleep disturbances reported by parents on the Post-Hospital Behavioral Questionnaire (PHBQ) collected during our "COPE, Improving Outcomes in Critically Ill Children" study using the control group. The parent study was a randomized control trial of 174 children admitted to the PICU to determine the effectiveness of the COPE Program on critically ill young children and their mothers. The control group was selected for analysis because it most closely represents an unsolicited population of children admitted to the PICU. For these patients, we calculated a sleep disturbance subscore from the sleep questions on the PHBQ. These questions include maternal reports of fussiness about going to bed, frequency of bad dreams, fear of the dark, bedwetting and trouble getting to sleep at night. Numerical values were assigned to parental responses of much less than before (1), less than before (2), same as before (3), more than before (4) and much more than before (5). Thus, scores >3 represent increasing sleep disturbances following hospital discharge. Statistical reliability of subscores was established (α>0.7). Data was analyzed using standard parametric statistical tests. Statistical significance was taken at the $p<0.05$ level.

Results: 76 children were enrolled in the control group. Of these, 40 subjects had information from the PHBQ at 1 month post-discharge while 25 subjects were still enrolled at 12 months after discharge. Of these 40 children, 65% were male, 80% were Caucasian and their mean age was 53.89 ± 20.07 months (SD). These subjects had a mean PICU length of stay of 75.76 ± 65.14 hours and a total hospital length of stay of 7.58± 5.66 days. When compared to pre-hospitalization sleep habits, study children had significant disturbances in sleep habits up to 12 months after discharge ($p<0.05$). Mothers reported disturbances in all queried aspects of sleep except for frequency of bedwetting at 1,3 6, and 12 months following discharge from the hospital when compared to pre-hospitalization($p<0.05$). Changes in sleep habits were not correlated with age, sex of the child, PRISM score, PICU or hospital length of stay (p=n.s.).

Conclusion: Even with decreasing length of stay along with better nursing and medical care that has transpired in today's PICU, children still experience significant sleep disturbances after discharge. Parental education about these effects is warranted. Assessment for possible sleep disturbances, with potential treatment may be important for children after discharge from the PICU. Further studies are needed to determine how PICU admission affects sleep after discharge, and to develop interventions to ameliorate the effect of PICU admission on sleep patterns after discharge.

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Sleep-Related Childhood Night-Time Crying "Yonaki" In Japan - Status As Sleep Problems And Influences On Mothers

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Introduction: In Japan, "Yonaki" or sleep-related childhood night-time crying (SRNC), which resembles night waking in Western countries, is frequently observed and parents are known to become exhausted because of insufficient sleep. The background mechanisms of SRNC as a type of sleep disorder and appropriate interventions remain unsolved. The present study aimed to examine the actual status of SRNC as a sleep problem and effects on maternal emotional state.

Methods: This developmental cross-sectional study recruited parents of 30 infants (3-6 months of age), 112 toddlers (18-21 months) and 82 preschoolers (36-41months) who were identified as suffering symptoms of SRNC. We defined SRNC as unexplained crying during the night on a frequent basis beyond the infancy period. Our questionnaire was administered to parents while attending a well baby checkup in Tokyo. Our questionnaire addressed aspects of the severity of SRNC by examining the temporal peak, frequency, maximum time duration and number of episodes, auxiliary behaviors, methods of parental intervention, which parent or family member interacts typically with the child, maternal emotional response to the condition, and with whom mothers discuss her child's SRNC.

Results: We have found that SRNC has not fully developed during the infancy period (Fukumizu et al., submitted), hence, parents of toddlers and preschoolers only were asked to identify the age at which SRNC occurred most frequently. The peak developmental period identified for SRNC was greater than 1 year of age but had declined considerably by 2 years of age. In this SRNC sample, the incidence of current SRNC occurring >1 episode per night in each group was 51.7%, 62.6% and 52.6% respectively. Crying bout duration >15 minutes was seen in fewer than half of the children (group differences were not statistically significant: infant= 26.7%, toddler= 45.0%, preschooler=50.6%). Regarding the behavioral context, parents were asked whether eyes open or not while crying. Few infants had eyes open. Most children (60.7%, 49.1%, and 57.5%) during SRNC had their eyes closed until crying was terminated. Across groups, 99.6% of children required parental intervention to terminate crying. Other signaling behaviors during crying episodes were more frequent at younger ages (infant=92.6%, toddlers= 94.6%, preschooler= 78.0%) ($p<0.005$). Children generally settled after an SRNC episode with intervention from additional adults besides the mother (35.7%, 62.2% and 48.1%, respectively), a difference that was significant between infancy and toddlers was significant ($p<0.02$). The manner of intervention was individual and no single solution was more prominent. Most mothers reported that they felt emotional strain when SRNC episodes occurred. Mothers who sought out psychosocial support or informational sources reported feeling better about their child's SRNC.

Conclusion: SRNC in Japan seems to have similarities to night waking in sleep disordered children in Western countries. Most of children with SRNC begin crying with eyes closed. We speculate SRNC is related to immature sleep regulation in some children which affects the incidence of night-time behavioral arousal and sleep continuity. Mothers reported emotional strain which was alleviated by talking with someone or referring to informational sources but did not consult formal medical or social services.

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Cognitive and Behavioral Functioning Associated with Sleep Disordered Breathing in Children Scheduled for Adenotonsillectomy in Comparison to Controls

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Introduction: Obstructive sleep-disordered breathing (SDB) in children is associated with deficits in academic achievement, attention, and problem solving. Childhood SDB is usually treated by adenotonsillectomy (AT), which is among the most commonly performed surgical procedures in children. Among indications for AT, the most common are SDB and recurrent tonsillitis, but even children in the latter group sometimes prove to have SDB. Therefore, we studied the range and extent of cognitive and behavioral problems among children scheduled for AT, for any clinical indication, in comparison to subjects scheduled for hernia repair, other procedures, or outpatient appointments.
Methods: Seventy-nine children scheduled for AT, with a mean age of 7.7 years (range 5 - 12; 57% male) were compared to a control group of 17 children undergoing hernia repair and 10 children seen at the same health system for reasons also unrelated to breathing or sleep (control group n = 27; mean age = 8.7 years; 70% male). Well-validated neuropsychological assessments were performed several days prior to treatment for the AT and other surgical participants.
Results: Analyses of variance for group (AT vs. control) and age (5 - 8 years vs. 9 - 12 years) demonstrated that children scheduled for AT, in comparison to control children, showed poorer functioning on objective measures of non-verbal/visual spatial skills ($p < .02$) and simple reaction time ($p < .001$). No differences were found in measures of vocabulary, list-learning, learning and memory for word pairs, visual abstract reasoning, fine-motor coordination, reading, or written expression. In addition, parent-completed measures of childhood problem behaviors revealed that AT children were more likely to demonstrate inattention ($p < .01$), hyperactivity ($p < .02$), oppositional behavior ($p < .02$), and inattention-related cognitive and learning problems ($p < .001$).
Conclusion: These results suggest that many children who undergo AT, most often without formal sleep or neuropsychological testing, frequently have deficits in cognitive functioning and problems with inattention, hyperactivity, and oppositionality. The pattern of these deficits is similar to that seen in dysfunction in the prefrontal cortex, consistent with known effects of sleep deprivation and SDB.

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Executive Dysfunction in Children with Sleep Disordered Breathing

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Introduction: In adults, sleep disordered breathing (SDB) has adverse effects on executive functioning, the cognitive processes that facilitate flexible, future-oriented, and organized behaviors. This study used comprehensive tests and questionnaires to investigate the executive functioning of children with varying levels of SDB, as compared to healthy controls and published norms. Based upon adult findings, we hypothesized that children with SDB would show deficits in executive functioning, but not IQ or memory.
Methods: The CLINICAL GROUP was comprised of 33 children aged 6-12 who underwent laboratory polysomnogram (PSG) because of clinical symptoms of SDB. The CONTROL GROUP was comprised of 17 age- and gender-matched children who were recruited via door-to-door solicitation in the neighborhoods in which a clinical child lived. PSG was not conducted on controls, but controls neither snored regularly nor had witnessed breathing pauses. Exclusion criteria for both groups included neurological comorbidity or use of psychotropic medications (except psychostimulants, which were discontinued 24 hours prior to testing and PSG). All children underwent cognitive testing and we collected parent and teacher questionnaires. DEPENDENT MEASURES included intelligence (2-subtest WISC-III), memory (WRAML list learning), executive functioning (WISC-III Digit Span, NEPSY Visual Attention and Verbal Fluency, Gordon CPT Omissions and Commissions; also in children 8 and older the WCST and Stroop Interference Test), and questionnaire measures of attention, behavior regulation, and executive functioning (BASC, BRIEF).
Results: The groups did not differ in age, gender, or ethnicity. Mean age was 9.9 (sd=2.2) yrs; 60% were boys; 68% were Caucasian, 28% were African-American. The clinical group had higher SDB symptoms on Owens' Child Sleep Habits Questionnaire (CSHQ $p<0.0001$). However, the clinical group also had lower income ($p=0.05$) and parent education ($p=0.001$). Because intelligence and many questionnaire subscales correlated with family income and parent education, we covaried for these in relevant analyses. Using MANOVA and MANCOVA, the groups were compared on predetermined sets of dependent measures (alpha=0.05 in each set). The clinical group performed more poorly than controls in visual scanning, impulse control, and verbal fluency. The clinical group also performed worse on parent-report of attention, behavior regulation, and executive functioning, but not on analogous teacher-report measures. Scores of the clinical group were then compared to norms using z-tests (1-tailed alpha=0.005). The clinical group scored worse than norms in visual scanning, impulse control, verbal fluency, and parent- and teacher-report of attention, behavior regulation, and executive functioning. The clinical group scored neither poorer than norms nor poorer than controls in intelligence, memory, short-term or sustained attention, or concept-formation. Finally, those measures which were weak in the clinical group were correlated with PSG indexes (AHI, Respiratory Arousal Index, O2 Desaturation Index, % of sleep with $SaO2 < 80\%$, Sleep Efficiency) and parent report of SDB symptoms on the CSHQ (1-tailed alpha=0.005). No PSG index correlated with any dependent measure. SDB symptoms correlated with visual scanning, verbal fluency, parent-report of disinhibition, and teacher-report of inflexibility and aggression.
Conclusion: Aspects of executive functioning appear to be particularly vulnerable to SDB in children. The mechanisms underlying this vulnerability remain unclear.

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Cortisol Plasma Concentration Throughout The Night Increases Slowly In Formerly Iron Deficient Preadolescents

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Introduction: Iron is critical for several brain functions including neurotransmission systems, myelination, and neuronal metabolism. Iron deficiency anemia (IDA) in infancy, is associated with long-lasting

behavioral, neurofunctional, cognitive, and sleep organization effects, despite the correction of anemia with iron treatment. Hormonal regulation is also affected in iron deficient conditions. Thus, it is conceivable that sleep hormonal regulation alterations may be apparent as well. Since the cortisol rhythm is considered to be a marker of the temporal organization, with an abrupt rise in the second half of the night and an early morning acrophase, we assessed the nocturnal cortisol plasma level in former IDA (FIDA) preadolescents.
Methods: Polysomnographic recordings and a 20-min blood sampling procedure were continuously performed during the night in 31 healthy 10-y Chilean children (FIDA= 18, control= 13). Both groups have been followed from infancy and are comparable for well known confounding and intervening variables, such as socioeconomics, maternal characteristics and home environment. Plasma cortisol was determined by electrochemiluminiscence (Roche, Basel, Switzerland). For the individual subject, mean cortisol values were calculated for each successive third of the sleep period time (SPT).
Results: The SPT was similar in both groups, whereas mean cortisol values were significantly higher in controls compared with FIDA preadolescents in the 2nd (133.6 vs. 84.9 nmol/L, $p<0.01$) and 3rd (256 vs. 184.2 nmol/L; $p<0.05$) thirds of the SPT.
Conclusion: During a spontaneous sleep episode, FIDA preadolescents were characterized by lower concentration of plasma cortisol with advancing time during the night relative to controls. These results suggest long-lasting hormonal effects. If these findings hold up with the full sample, a lower cortisol level upon waking could reduce the alerting tone in FIDA preadolescents.

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Evidence for Maturational Changes in Process S during Adolescence Based on Empirical Data and Simulations

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Introduction: The delay in the timing of sleep is a dramatic behavioral change of adolescents. Teenagers tend to stay up late at night and sleep late in the morning compared to preadolescents. In addition to modifications of the circadian clock during puberty, developmental changes of the sleep-dependent homeostatic process (Process S) may contribute to the adolescent sleep delay. Our aim was to examine whether pre-pubertal children and mature adolescents differ in the dynamics of Process S from analysis of slow-wave activity (SWA, EEG power in 0.6-4.6 Hz band) in NREMS.
Methods: After at least 10 nights on a fixed 10-h sleep schedule, sleep was recorded in 12 healthy children under baseline conditions and during recovery from a 36-h constant routine procedure involving total sleep deprivation. Six children were classified as Tanner stages 1 or 2 (T1/2 = pre- or early pubertal; mean age 11.8±0.9 years, one boy) and six children as Tanner 5 (T5 = mature; 14.3±1.4 years, three boys). Sleep stages were scored according to conventional criteria. EEG power spectra (derivation C3/A2) were calculated. Each participant's mean SWA per NREMS episode was calculated as percentage of the mean nocturnal SWA. Parameters of Process S were estimated by minimizing the mean square error between simulations and empirical data (group mean SWA per NREMS episode). Simulations were based on 3 baseline nights followed by sleep deprivation and 3 recovery nights.
Results: A significant enhancement of NREMS EEG power during recovery compared to baseline was present in the SWA range of both T1/2 and T5. In T1/2 the increase of SWA comparing recovery to baseline was less pronounced (17 %) compared to T5 (40 %). A good fit between empirical SWA and Process S was observed in both T1/2 and T5. The time constants of the exponential decay of Process S were similar between developmental groups (3.0 h in T1/2 and 2.5 h in T5). The saturating exponential rise of Process S during wakefulness, however, yielded a markedly shorter time constant in T1/2 (7.7h) than in T5 (13.9h). The difference between upper and lower asymptote was smaller in T1/2 (301.5 %) compared to T5 (432.7 %).
Conclusion: These data indicate that sleep deprivation affects the sleep EEG in adolescents similar to young adults. The two-process model of sleep regulation accurately predicted the time course of SWA in pre-pubertal children and mature adolescents. While our results indicate that there are no differences in the nocturnal dynamics of Process S between the groups, Process S seems to increase at a different rate during wakefulness. We speculate that the pre-pubertal brain reaches its capacity to generate slow waves faster than the mature brain and thus limits the ability for pre-pubertal children to stay awake at the end of the day. This limitation also manifests as a reduced relative increase of SWA during recovery from sleep deprivation.

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Sleep Disorders And Starting Time To School Impair Fine Motor Coordination In 5 Years Old Children

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Introduction: Several studies have shown a probable negative influence of sleep disorders on cognition of school aged children, but few studies focus the possibility of motor abilities dysfunction in this age range. This study aims to verify if children with sleep disorders present dysfunction in fine motor coordination, and also to verify the influence of the starting time to school, as circadian rhythm could increase the effect of the sleep disorders on motor and cognitive functions.
Methods: We studied 272 five years old children from public schools of Sao Paulo City, SP, Brazil. The sleep disorders group (SDG) was identified by a sleep questionnaire (Bruni et al, 1996) adapted for Brazilian Portuguese language. Starting time to school enrolled were Morning (07:00AM finishing at 11:00AM); Intermediate (11:00AM finishing at 3:00PM); and Afternoon (3:00PM to 7:00PM). The SDG had 102 (58 boys) children with disorders of initiating and maintaining sleep, disorders of arousal, sleep breathing disorders, disorders of excessive somnolence, sleep hyperhydrosis, and sleep wake transition disorders. The control group (CG) had 170 children (86 boys). To evaluate fine motor coordination, we request to the children to make a simple knot in a pedagogical shoe. We classify as a success in the test, if the children did the knot even with some difficulty. We consider fail if the children did not try the test or after some attempts did not make the knot. We compare the outcome success and fail for SDG and CG according to starting time to school (Morning, Intermediate and Afternoon). Qui-square and regression analysis were used to analyze the data.
Results: 385 questionnaires had been distributed, 115 had not been used because there were children with visual, osteomuscular and/or neurological preexisting deficits or children out of the age range and children that had refused to participate or had not appeared in the date of the test

application. Of 272 children, 144 (52.9%) were boys, 72 children studied in the morning, 104 studied in the afternoon and 96 children in the Intermediate. As a whole, there were no differences in the number of children that fail in the test according to the starting time to school. Boys and girls were not different as well, but when we added the starting time to school to the regression model we found that boys had more fail in the test ($p< 0.05$).
Conclusion: This study suggests that at least in some group of children, sleep disorders can interact with starting time to school allowing then to fail in some motor performance. We believe that five years old children studying in the afternoon failed in the test because they are deprived of some the still necessary afternoon sleep.

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Anterior-to-Posterior Shift of Sleep EEG Spectral Power Across Adolescence

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Introduction: In adults, EEG power decreases with age for frequencies below 15 Hz in NREMS and below 10 Hz in REMS. A similar decrease of low frequency power for NREMS and REMS is found at the transition from childhood to adulthood. Age also affects regional sleep EEG characteristics in adults through an anterior-to-posterior shift of theta power in both sleep states and alpha/sigma power in NREMS. Whether sleep EEG topography changes across adolescence, however, remains unknown.
Methods: After at least 10 nights on a fixed 10-h sleep schedule, sleep was recorded for 10 hours in 8 children Tanner stages 1 or 2 (pre- or early pubertal; mean age 11.2±1.0 years, four boys) and in 8 children Tanner stages 4 or 5 (late pubertal or mature; 15.1±1.3 years, three boys). Sleep stages were scored according to conventional criteria. EEG power spectra of 2 bipolar derivations along the anterior-to-posterior axis (midline; Fz/Cz = anterior and Pz/Oz = posterior) were computed and then matched with corresponding sleep states. Differences between derivations and between groups were assessed on log-transformed power density values (significance level $p<0.05$).
Results: The typical declining trend of EEG power with increasing frequency, as well as frequency-specific and state-dependent modulations of EEG power across the sleep episode were common features in the anterior and posterior derivations of both developmental groups. Further, an overall reduction of EEG power during NREMS and REMS in mature compared to pre-pubertal children extended over nearly the entire frequency range up to 30 Hz, most evident in the frequency ranges below 10 Hz. The reduction was not uniform over the two leads, however, but was most pronounced in the anterior derivation. Within group analysis of EEG power in NREMS showed that power across all bins in the 0.6-30 Hz range of the pre-pubertal children 's anterior lead was significantly greater than posterior. This anterior predominance was not observed in mature adolescents in any frequency range during NREMS. The REMS power distribution of pre-pubertal children was somewhat different. Although REMS EEG power in the high-delta (3-4.6 Hz), theta (5-6 Hz) and beta ranges (18-30 Hz) was predominant in the anterior lead, EEG power in the low delta (< 2 Hz) and alpha range (8-10 Hz) showed posterior dominance. Mature children manifested higher REMS EEG power in posterior derivations for the low-delta (< 2 Hz), theta, alpha and sigma ranges (7-14 Hz); no frequency range showed anterior predominance in REMS for the mature adolescents. Overall, these patterns indicate a shift to posterior EEG power dominance across adolescent development for both NREMS and REMS.
Conclusion: The state-independent anterior-to-posterior shift of sleep EEG power across adolescence may reflect developmental changes of the brain during puberty. Thus, for example, cortical gray matter increases until age 12 years in the frontal lobe and decreases thereafter, while the occipital lobe gray matter increases linearly from early childhood though adulthood. Hence, the anterior-to-posterior shift of sleep EEG power may indicate more pronounced synaptic pruning over anterior regions.

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Epidemiology of DSM-IV Insomnia among a Community-based Cohort of Adolescents

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Introduction: Epidemiologic study of insomnia among adolescents has been limited. The few studies examining the broader concept of disturbed sleep report prevalence that ranges from 6% to 27% depending on definition, sample, and period (past month to past 12 months). Likewise, studies of the association of disturbed sleep with adolescent characteristics and behaviors have produced varying results. There has been one epidemiologic study of insomnia defined by DSM-IV criteria among adolescents. Ohayon et al. (2000) reported a point prevalence of 4% among adolescents 15 to 18 years old in a European sample. In this study we examined the epidemiology of DSM-IV defined insomnia among a community-based sample of adolescents 13 to 16 years old.
Methods: Data come from a sample of 1014 youth and parent pairs randomly selected from all eligible households in a 400,000 member HMO in the Detroit metropolitan area. The response rate was 71.2%. The participation rate among contacted pairs was 81.3%. 50.3% of adolescents were female and ranged in age from 13 to 16, with a mean age of 14.4. 62.3% of adolescents identified themselves as White, 31.2% as Black and 6.2% as another racial/ethnic group. The median household income range was $60,000 - $69,999. Separate computerized structured interviews were conducted with each adolescent and one parent. Insomnia was defined according to DSM-IV criteria as a complaint of difficulty initiating or maintaining sleep, or nonrestorative sleep, at least twice a week, for a one month or longer resulting in significant distress or impaired function. Tanner staging was assessed by sex specific self-report scale.
Results: While 33.2% of adolescents reported insomnia symptoms in their lifetime, 16.8% met criteria for insomnia including distress/impairment. Girls reported a greater prevalence than boys: 19.6% of girls and 13.9% of boys (OR = 1.5, 95% CI 1.08 - 2.11). Prevalence of insomnia did not differ by race/ethnicity or marital status of parents, but there was a trend toward lower prevalence of insomnia with increased household socioeconomic status. Physical maturation was associated with increased risk of insomnia, adjusted for age, sex and race/ethnicity. The 3 higher quartiles of the physical maturation scale score showed similarly increased risk of insomnia compared to the to lowest, which was characterized by just having begun puberty (OR = 1.73 95% CI 0.94 - 3.18; OR = 1.77 95% CI 1.01 - 3.10; OR = 1.85 95% CI 1.05 - 2.34). The median age of onset of insomnia was 11 (interquartile range = 5). Of adolescents with lifetime insomnia, 94% reported experiencing insomnia symptoms twice a week for a month or longer during the past 12 months and 85% did so within the past month. 31.8% of adolescents with lifetime insomnia also had another DSM-IV psychiatric disorder.

Conclusion: Insomnia as defined by DSM-IV criteria appears to be highly prevalent among adolescents in the community, may be associate with the onset of puberty, and appears to be chronic or frequently recurrent for the majority of affected adolescents.

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Ambulatory Measurement of Periodic Leg Movements in Children With and Without Restless Legs Symptoms

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Introduction: Restless Legs Syndrome (RLS) is a chronic progressive neurological disorder typified by an irrepressible urge to move the legs accompanied with a sensory discomfort that is worse with inactivity and which intensifies in the evening. RLS symptoms disturb sleep and are associated with Periodic Limb Movements (PLMs) which also interrupt sleep. Recent epidemiologic and genetic linkage studies have begun to distinguish two forms of RLS; early onset (primary RLS), and late onset (secondary RLS). The early onset form typically begins in childhood or young adulthood, develops in a slowly progressive manner, is inherited in an autosomal dominant fashion, shows genetic anticipation, is more prevalent in females (2:1), and has been associated with distinct genetic loci in the human. PLMs are thought to be more prominent in this form. Identification of PLMs by overnight polysomnography (PSG) is costly and subject to inaccuracies due to the night-to-night variability of PLMs. In this study, we used a 5-day in-home accelerometer-based leg monitoring system to measure PLMs in children. The hypothesis that children with RLS symptoms have more PLMs than children without RLS symptoms was explored using this novel recording system.
Methods: Children were assessed for RLS symptoms and assigned to the RLS group or the no-RLS group prior to recording. RLS symptoms were determined using the four standard adult criteria for RLS: (1) a desire to move the extremities, usually associated with leg discomfort, (2) motor restlessness, such as pacing, tossing and turning, stretching, rubbing or heating/cooling the leg(s), (3) symptoms worse at rest and somewhat better with movement, and (4) symptoms are worse at night or in the evenings. In-home leg monitoring was performed to identify PLMs. A pair of ambulatory PAM-RL PLMs monitors (IM Systems, Baltimore, MD) was worn on each ankle over 5 consecutive nights. The IM System PAM-RL ambulatory leg monitor is a self-contained, programmable, micro-processor based tri-axial accelerometer with 10 Hz sampling. Data was downloaded in a graphic format for analysis. PLMs were defined by the International Classification of Sleep Disorders (ICSD) as four or more periodic episodes of repetitive limb movements occurring 0.5-5 seconds in length and separated by 4 to 90 seconds. An index of PLMs per hour was determined for each night and for the entire 5 night study. Analysis of PLM data were performed in a blinded fashion.
Results: Ambulatory leg monitors successfully recorded PLMs in 6 children with and 6 without RLS symptoms. Over 5 nights, the average PLM index was >5 in children with RLS symptoms and <5 in children without RLS symptoms. Night-to-night variability in PLMs was observed in both groups.
Conclusion: Measurement of PLMs in children can be performed using ambulatory leg monitoring. PLMs are more frequently observed in children with RLS symptoms. The increased length of recording time (5 days) employed by the use of ambulatory monitoring versus a single night PSG may enhance the overall sensitivity for recording PLMs. Additional studies using this technology to determine the prevalence of PLMs in children with and without RLS are underway.

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Sleep Patterns in an Urban Sample of U.S. School-Aged Children

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Introduction: Normative sleep behavior of school-aged children, particularly of minority ethnicity, is not well documented. The U.S. National Sleep Disorders Research Center has called for these data to develop sound recommendations for children's sleep. Understanding the sleep behaviors of pre-adolescents may be particularly useful for developing strategies for preventing sleep restriction in teenagers, a group who often sleep too little, are sleepy, and are at increased risk for sleep-related car accidents. Our objective was to describe the sleep behavior of a community-based cohort of 8-11 year-old children participating in the Cleveland Children's Sleep and Health Study, and assess variations by age, sex, and ethnicity.
Methods: Sleep patterns and health data were ascertained from a child-completed 7-day sleep journal, the Children's Health Questionnaire-PF50, and the Children's Sleep and Health Questionnaire. Outcome variables included: mean sleep duration over the recording period and bedtime 23:00 or later. Linear regression was utilized to assess effects of age, sex, ethnicity on mean sleep duration adjusting for potential confounders (preterm status, chronic health/behavioral problems, caregiver's education, sick/vacation days). Logistic regression was used to estimate the odds of bedtime 23:00 or later, controlling for potential confounders.
Results: The sample of 755 children was 50% female, 35% ethnic minorities (mostly African-American), 94% with a primary caregiver completing high school or more, and had a mean age of 9.5 ±.79 [SD] years. The mean bedtime was 22:05±0.81 [SD in hours], mean waketime was 07:42±0.87, mean sleep duration was 9.63±0.72 hours. 16% of the sample reported getting less than 9 hours of sleep. Univariate results showed a significant effect of age group ($p<0.0001$), whereby mean sleep duration of 10-11 year-olds (9.45±0.81) was significantly shorter than that of 8-year-olds (9.74±0.68) or 9-year-olds (9.65±0.68); boys had significantly shorter sleep duration than girls (9.50±0.71 vs. 9.61±0.72, $p=0.030$); and minority children tended to sleep less, on average, than non-minority children (9.45±0.86 vs. 9.61±0.63, $p=0.070$). 43% of 10-11 year-old minority boys reported less than 9 hours nightly sleep, versus 5-26% of other age-ethnicity-sex subgroups. Adjusted results showed that oldest minority boys had the shortest mean sleep duration: 9.28±.07(SE) hours, compared to 9.43 to 9.85 hours for the other age-sex-ethnicity subgroups. At all ages, minority boys slept significantly less than non-minority boys ($p=.002$) and girls ($p=.0004$), and minority girls ($p=.004$). Mean sleep duration among the other three ethnicity-sex groups was not significantly different. After controlling for confounding, minority children had 4.8 times the odds (95% CI: 2.9,8.0) of a bedtime 23:00 or later compared to non-minority children.
Conclusion: Use of self-completed 7-day sleep journals provided mean estimates for sleep duration consistent with current national recommendations for school-aged children. A large minority of middle-school children, however, sleep less than the recommended 9 hours. Across the age range 8-11 years, significant decreases in sleep time and, in ethnic minorities, increasingly delayed bedtimes were observed, suggesting the emergence of sleep restriction patterns in pre-adolescents. The shorter sleep durations in ethnic minority boys highlights the need for (1) better understanding of the social and environmental influences encouraging this sleep pattern; and (2) sleep-hygiene interventions targeting specific groups of school-aged children.

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Delta EEG Evidence that Adolescent Brain Maturation Begins Earlier in Girls

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Introduction: Slow wave (delta) EEG within NREM sleep declines steeply across adolescence. We have hypothesized that this decrease is one element of a late brain maturational change that includes declines in synaptic density and cerebral metabolic rate. We compared baseline nighttime EEG of 9 and 12 year olds of both genders to determine whether the NREM delta power decline differs between boys and girls.
Methods: Seventy young subjects (32 - 9 year olds and 38 - 12 year olds) are participating in a 4 year longitudinal study of sleep EEG changes across adolescence. The data in this abstract are cross-sectional. The data are from the first recordings of 40 subjects, 10 of each age and gender. All subjects were studied in their own homes on their habitual sleep schedules with Grass H2O recorders. Hardware filters were 0.3 Hz low frequency and 100 Hz high frequency. The digitized (200 Hz) EEG signals were analyzed off-line with the power spectral and period amplitude analysis components of the PASS PLUS (Delta Software) EEG analysis system. Visual scoring was performed on computer display of the digitized data. Sleep state durations and NREM delta (0.3-3 Hz) EEG power were compared among the 4 age-gender groups.
Results: Total sleep time was lower in the 12 year olds than in the 9 year olds (474 +/- 10 min vs. 522 +/- 8 min, $p<0.0005$). Although average total NREM delta power and delta power per min of NREM sleep were lower in the 12 year olds (by 20% and 13% respectively), the differences did not reach the 0.05 significance level. Examining the genders separately showed that delta EEG was lower in the girls but not in the boys. Total delta power in 12 year olds girls was 37% ($p=0.01$) lower than in 9 year old girls. In contrast, total delta power did not differ in 12 and 9 year old boys ($p=0.96$). Delta power per min of NREM sleep was 29% lower in 12 year old girls than in 9 year old girls ($p=0.03$) and 27% lower in 12 year old girls than in 12 year old boys ($p=0.03$).
Conclusion: These data suggest a sexual dimorphism in brain maturation during early adolescence such that the decline of delta EEG power begins earlier in girls than in boys. The cross-sectional data presented here are a random sample from the first of 8 semiannual longitudinal recordings of these two age cohorts. In future years, our longitudinal studies will enable us to describe the maturational change within individuals. We will also determine whether these brain changes correspond in time to sexual maturation (Tanner stages) and other measures of biobehavioral development.

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Cardio-Respiratory Sleep Indexes - A New Simple Method for Pediatric Obstructive Sleep Apnea Screening and Cardio-Sleep Quality Study

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Introduction: The cost and inconvenience of standard polysomnography (PSG) for obstructive sleep apnea (OSA) has stimulated studies for an alternative diagnosis method. The development of in-home OSA testing appears to be particularly well suited to the pediatric population for which the prevalence of this disorder is only now being appreciated. For this purpose, a new robust method was developed based on heart beat intervals (HBI). This method, using simple time domain techniques that do not have the need for HBI stationarity or the resampling of HBI, is able to provide the important and necessary information for pediatric OSA studies.
Methods: A set of cardio-respiratory sleep indexes (CRSI) were developed and tested on a database of pediatric patients that have under gone a full PSG evaluation. These indexes estimate mean respiratory rate, the standard deviation of the rate, and unique changes in respiratory pattern. According to the different sensitivity and robustness of each index to HBI pattern and variability, thresholds for each index can be set and applied equally to all subjects. Five healthy developmentally appropriate pediatric patients (age: 8.6 /- 3.0), without any congenital defects were selected from a recent MRSDC-HCMC database. The PSGs were indicated in each instance as an integral part of determining both the perioperative risk and eventual appropriate post-operative management for an anticipated tonsillectomy/adenoidectomy. Of the five patients, three were seen to have significant OSA (apnea/hypopnea index (AHI) 4.9, 4.4 and 44) based upon the formal PSG in accordance to standard guidelines for scoring pediatric obstructive sleep disordered breathing. The overnight data were segmented by a moving window of 150 seconds. Each segment was labeled as respiratory disturbance contaminated if there was at least one apnea/hypopnea event (according to PSG), one visual respiratory disturbance or one visual EEG arousal. Therefore 300 out of 1142 segments were identified as the targets for the detection based on HBI.
Results: The overall sensitivity and specificity of the detection using CRSI was 68% and 88.3% respectively. The sensitivity and specificity was 78% and 85.7% respectively for OSA group. Cyclic variation of heart rate (CVHR- the feature of severe OSA events) patterns was detected in each OSA patient by CRSI, while no CVHR detected in normal subjects.
Conclusion: This study demonstrates that CRSI is a promising method for pediatric OSA screening. CRSI results showed a strong correlation between stable respiration and NREM sleep. Results also suggest the possibility of using different degrees of CRSI variances for stratifying normal NREM, REM, respiratory disturbances, arousals or severe OSA events during sleep. Unlike other HBI methods, CRSI directly reflects the dynamics of the state or homeostasis of the cardiovascular system and gives values in terms of meaningful physiological units. This can provide some new information on the interactions between cardiovascular system and respiration during sleep. A refined detection algorithm and program based on CRSI is being developed and will be tested on a large pediatric PSG database at MRSDC-HCMC.

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Sleep Disorders: Age Makes a Difference

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Introduction: Normal sleep is vital to the process of somatic growth and neurological development. Moreover, sleep disorders (SD) can affect cardiovascular health, cognitive functioning, and lead to behavioral problems. Given that it is estimated 20% to 25% of children/youth experience some type of sleep disturbance, it is essential to understand sleep problems and their manifestations within different age groups. The clinical signs and symptoms observed in children/youths are variable within age groups, and frequently differ from those exhibited by adults. Additionally, SD in this population may be related to a medical or psychiatric issue yet to be fully addressed. For example, children with sleep disordered breathing (SDB) or periodic limb movement disorder (PLMD) may display symptoms characteristic of attention-deficit/hyperactivity disorder (ADHD), such as inattentiveness, hyperactivity, and aggressive behaviors. If a child/youth is diagnosed and medicated for ADHD without receiving judicious assessment for a possible underlying SD, unnecessary medications may be prescribed, and the SD will prevail. As is the case in adults, SD in children/youth are underreported and under diagnosed. However, for optimal somatic growth and neurological development it is essential that SD in children/youth be addressed. Accordingly, we investigated children/youth SD in general and compared the findings with an adult sample.
Methods: We assembled a team comprised of professionals from a broad spectrum of specialty areas and constructed a 92-item patient questionnaire and a 12-item questionnaire for children/youth to assess both the children/youth and the caregiver perspectives and also constructed a 111-item questionnaire for adults. We designed these measures to assess sleep habits, sleep observations, past medical history, prior treatment approaches for SD, social information, and medications. We used the questionnaires in conjunction with other standard patient questionnaires, nocturnal polysomnography (NP) studies, multiple sleep latency tests (MSLT), and medical chart reviews of patients with SD. We then constructed a database comprised of 305 measures collected in 13 categories
Results: We compared age appropriate data for 25 children/youth [average age 11.14 (range, 1-17), 10 females, 15 males] with a sample of 291 adults [average age 52.02 (range 18-88), 112 females, 179 males]. Analyses comparing findings from children/youth with adults revealed both patterns of similarities and differences. For example, proportionally, children/youth were more likely to have diagnoses of CNS abnormalities $X2(1, N = 283) = 5.653$, $p = .017$); children/youth were more likely to have a disability ($X2(1, N = 261) = 12.656$, $p = .000$); adults were more likely to be obese ($X2(1, N = 299) = 33.684$, $p = .000$); and children/youths were more likely to be diagnosed with a mental disorder, other than ADHD, $X2(1, N = 264) = 9.139$, $p = .003$).
Conclusion: Our analyses revealed some similar and some different patterns when comparing children/youth with adults. Indeed, opposite patterns exist, further emphasizing the critical need to explore age specific characteristics in SD.

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Transcutaneous Carbon Dioxide Monitoring and Capnography During Pediatric Polysomnography

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Introduction: Transcutaneous monitoring and capnography are two surrogate methods of measuring arterial carbon dioxide levels employed by pediatric sleep laboratories. Both techniques are non-invasive, validated and quantitative indirect predictors of arterial carbon dioxide level and both have been widely adopted for use during pediatric and adult polysomnography (PSG). A thorough comparison of these tools in pediatrics has yet to be performed. We reviewed our experience using transcutaneous and end-tidal carbon dioxide monitoring in 217 children with respect to the total amount of time reliable signals could be obtained from both devices during overnight PSG and the correlation between the two outputs.
Methods: A sample of children referred for diagnostic polysomnography to the Pediatric Sleep Laboratory at Alberta Children's Hospital from October 1999 to October 2003 were included. All patients underwent an overnight-computerized PSG as per American Thoracic Society standards. Transcutaneous and end-tidal signals were both included in our standard montage. A registered PSG technician manually scored studies and eliminated all CO2 data that was not reliable based on predetermined criteria of acceptable values and signal waveform clarity. Total 'bad data' time was calculated for both channels.
Results: 217 children (128 males), mean age 7.1 ± 4.6 years (range 0.1 - 18.2), were studied. The average Total Recording Time (TRT) was 460.1 ± 62.2 minutes (range 155.4 - 565.1). On average, reliable data was simultaneously obtained from both channels for 49.2% ± 39.2 of the time. The mean duration of 'bad data' per night respectively for the transcutaneous and end-tidal was 178.9 ± 149.6 minutes (0.0 - 565.1) and 232.8 ± 187.5 minutes (0.2 - 565.1). When both signals were compared the CO2 maximum values agreed within 1.0 ± 6.0 mmHg and the C02 mean 0.1 ± 4.0 mmHg.
Conclusion: Transcutaneous and end-tidal carbon dioxide monitoring during polysomnography are well tolerated and provide reliable and comparable results in the majority of children.

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Obstructive Sleep Apnea Treatment and Weight Change Among Pediatric Patients

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Introduction: Childhood obesity has increased threefold (5% to 15%) over the last three decades. Significant association between childhood obesity and sleep disordered breathing witn an approximate odd ratio of 5 has been reported. While obstructive sleep apnea (OSA) treatment should improve daytime function and activity, no study has systematically examined the impact of effective OSA treatment on weight change in the pediatric population. This study aimed to retrospectively review the body mass index (BMI) changes of pediatric patients successfully treated for OSA with adenotonsillectomy and/or continuous positive airway pressure (CPAP) therapy.
Methods: Patient records from January 2000 to June 2003 were retrospectively reviewed. Children with OSA based on baseline overnight polysomnogram were included. BMI at the time of, and 6, 12 and 18 months after OSA treatment were recorded. Three patient groups were identified: morbidly obese (BMI>37 kg/m2),obese (BMI>/=30kg/m2 but </=37kg/m2),and those with BMI <30 kg/m2.

Results: Seventy-five patients (50% male and female) were included with mean age of 10.3 +/- 4.6 years (range 2-19 years). Thirty (40%) patients had BMI<30kg/m2; 12 (16%) were obese and 33 (44%) were morbidly obese. The mean BMI at time of OSA treatment was 36.1+/-18kg/m2 and the mean respiratory disturbance index (RDI) was 20+/-23. Only 20 (44%) patients who were obese or morbidly obese were involved in regular exercise programs; 17 (35%) were involved in diet programs. In one-way analyses of variance (ANOVA), children who were in the morbidly obese group were older and had a greater number of co-morbidities compared with the other two groups (each $p<0.001$). There was no difference in RDI by BMI category or gender. Patients who were obese and morbidly obese were more likely to require CPAP therapy alone or in combination with adenotonsillectomy (chi-square=38.4 $p<0.001$). In repeated measures ANOVA controlling for age, change in BMI over time (6 and 12 months after OSA treatment) varied across the 3 BMI groups (multivariate test $p=0.043$). The estimated marginal means for the time-by-BMI group interaction indicated that BMI did not change from baseline in the BMI<30kg/m2 group at 6 and 12 months; increased between 6 and 12 months in the obese group, and decreased in the first 6 months but then increased by the 12-month assessment in the morbidly obese group.
Conclusion: Obesity and its associated co-morbidities remain a problem in obese children in spite of effective OSA treatment. Following OSA treatment, a decrease in BMI was observed in the morbidly obese group in the first 6 months after treatment followed by a gain in BMI by 12 months, but the cause of this decrease cannot be attributed to OSA treatment absent an experimental design. Specific interventions targeting weight control should be emphasized in the overall management of obese children with OSA.

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Effects of Acute Sleep Restriction on Respiration and Sleep Architecture in Children With and Without Obstructive Sleep Apnea Syndrome

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Introduction: Little is known about the effects of acute sleep restriction (SR) on breathing and sleep in children. The aim of this study is to use an acute sleep restriction challenge in children who have Obstructive Sleep Apnea Syndrome (OSAS) and an age matched healthy comparison group to better understand the impact of insufficient sleep on the sleep architectures and sleep related respiratory function. We hypothesized that: 1) both groups will show change in sleep architecture including, fewer arousals, decreased NREM stages 1&2 and REM and increased NREM stages 3&4; 2) sleep related respiratory dysfunction will worsen in both groups with a more negative impact on the OSAS subjects.
Methods: Subjects: Three OSAS patients (2 male, 1 female, mean age 8.3 year (SD= 1.5)) and 4 healthy controls (3 male, 1 female, mean age 10 year (SD= 0.0)). Standard polysomnography was conducted on all subjects at baseline and a sleep restriction night for which they were allowed to sleep for a maximum of 4 hours between 4 and 8 am. All studies were scored by 3 investigators using R&K sleep staging and American Thoracic Society childhood OSA event scoring criteria.
Results: Given that this is a pilot study with a small sample, no statistical analysis was conducted. Mean sleep study results at baseline and SR are reported for both groups. In the control groups: Increased sleep efficiency 91%(SD=4.0) versus 96%(SD=2.5), decreased sleep latency 19min(SD=15) versus 3min (SD=1.8), decreased arousal index (#/hr) 8.3(SD=2.4) versus 8.0(SD=2.6), decreased REM latency 146min versus 115min, decreased stage 1-2 sleep 64%(SD=8) versus 55%(SD=11) and REM sleep 14%(SD=5) versus 5%(SD=5.5), increased Stage 3-4 18%(SD=1.8) versus 36%(SD=6.8), increased periodic limb movement index (PLMI) 1/hr (SD=0.5) versus 5/hr(SD=3.5), no change in respiratory disturbance index(RDI)0.08(SD=0.15) versus 0.00(SD=0.00); In the OSAS group: increased sleep efficiency 89%(SD=3.1) versus 96% (SD=1.8), decreased sleep latency 17min (SD=5.9) versus 3min (SD=1.3), decreased REM latency 153min versus 133min, decreased arousal index 7.2/hr(SD=1.3) versus 4.9/hr(SD=4.1), decreased Stage 1-2 63%(SD=7.3) versus 42%(SD=6.8) and REM 15%(SD=2.7) versus 5%(SD=6.3), increased stage 3-4 22% (SD=6.6) versus 50%(SD=9.7), decreased PLMI 2.4/hr versus 6.3/hr, increased respiratory disturbance index 4/hr(SD=1.1) versus 16/hr(SD=11), apnea index in REM 9.8(SD=12) versus 11(SD=9), hypopnea index in REM7.7(SD=6.9) versus 12(SD=14).
Conclusion: In general, 4 hours of sleep restriction appeared to have a significant impact on sleep architecture in both groups. Children with OSAS have relatively normal sleep architecture compared with normal controls at baseline. As predicted all subjects had increased slow wave sleep after the acute sleep restriction, with decreased stage 1 and 2 NREM sleep and REM sleep. During the SR night all subjects had an increased PLMI, while only OSAS subjects had an overall increase in their RDI and associated increases in RDI during NREM stages 1&2 and stage REM. This study suggests the sleep restriction and deprivation may worsen sleep related respiratory function in OSA subjects. This may also have implications for the timing and duration of PSG assessments.

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Continuity and Discontinuity of Sleep-Wake Behavior from the Neonatal Period to the Second Year

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Introduction: The developmental maturation of sleep-wake organization and its circadian control is rapidly defined during the first two years of life. This process is influenced by the cultural context, parental socialization and child temperament. In this longitudinal study, sleep-wake behaviors were examined between 6 weeks and 24 months for individual differences and trait stability. Sleep-wake state characteristics were compared to laboratory and parental assessments of developmental level, temperament, feeding, sleeping arrangements and parental practices regarding bedtime routine.
Methods: Participants (N=120) were identified during mid-pregnancy as part of a larger longitudinal project. Eligibility was restricted to pregnant women with low-risk, singleton pregnancies and a healthy full-term infant. Infants were assessed at three time points: 6-weeks, 16 months and 24 months of age. At Time 1 (6 weeks), sleep and waking across 24 hours were examined using the Baby Day Diary for 3 consecutive days in the home. Sleep, waking, crying, fussiness and feeding were recorded at 5-min. intervals across 24 hours. This method produced a record of the distribution and proportion of different behavioral states. Assessments of developmental level and temperament were completed at six weeks in the laboratory during a videotaped session of the motor scale of the Bayley Scales of Infant Development II (BSID). Temperament was assessed during the session by tabulating fussing and crying episodes, as well as ratings of infant consolability, alertness and activity level. Parents separately completed the Infant Characteristics Questionnaire (ICQ), which yields sub-scores of difficult-fussy, inadaptable, dull and

unpredictable. At Time 2 (16 months), parents completed the Sleep Habits Inventory, a Likert-style measure of the past week using sleep hygiene, onset, continuity, night-waking, parent-seeking, bed sharing, and use of sleep aids, during a telephone interview. Sleeping arrangements, naps, bed and wake-up times were also measured. The Physical Activity Scale and Infant/Toddler Symptom Checklist (SC) and subscores were used to assess temperament at 16 months. At Time 3 (24 months), the Baby Day Diary was repeated again for 3 days.
Results: Structural Equation Modeling (SEM) was used to examine the cross-age hypotheses for sleep-wake behavioral stability. Difficult temperament at 16 months is associated with 6 week parental ICQ ratings of fussiness and diary measures of fussiness at 6 weeks, but less robustly with the 24 months diary fuss measures. Preliminary findings suggest that sleep propensity and wakefulness at 6 weeks and 24 months is a conserved trait. Daytime sleep in infancy predicts sleep regulation at 16 and 24 months. Wakefulness at 24 months is associated with sleep disturbance at 16 months.
Conclusion: Sleep-wake behavior shows stability from infancy to early childhood, most strongly related to propensity towards sleep or wakefulness. Difficult temperament assessed at 6 weeks is consistent with 16 month SC scores, but not consistently predictive of problems with sleep regulation.

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Parental Perception of Childhood Sleep Disordered Breathing
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Introduction: Parental perception of their child's health is essential in the screening and work up of most pediatric illnesses. Health care workers rely on what parents tell them in order to direct their clinical decision making. Parental perception of pediatric hearing loss and balance has been studied, and it has been demonstrated that parents are poor predictors of objective data. Sleep disordered breathing (SDB) is another pediatric problem that relies on the history given by the parents to direct further work-up, and it is not known if parental perception correlates with clinical disease. It is important to identify and treat SDB expeditiously as it is associated with several morbidities including behavioral disorders, developmental and cognitive delay, cardiac problems, and failure to thrive.
Methods: Children age 2-12 years old who were referred for a sleep study between 5/2003 and 8/2003, whose parents completed the standardized questionnaire, and who underwent at least one half of the sleep study with out the use of CPAP/BI PAP were eligible for this study. Parents were asked to grade the severity of their child's sleep breathing disturbance (none, minimal, mild, moderate, or severe). Patients underwent a full polysomnograph (PSG) including recording of airflow (PTAF), respiratory effort, oxygen saturation, and end tidal pCO2. A retrospective chart review was conducted, and data points were collected from the parental questionnaire and the PSG. This study was approved by the affiliated Baylor IRB.
Results: Ninety five patients (66 males) were eligible for the study. The mean age was 7.2 years. Sixty eight percent of parents said their child had breathing problems during sleep. When asked to classify the severity of the breathing problem, 31% responded no problem, 14% responded minimal, 27% responded mild, 22% responded moderate, and 6% responded severe. Forty three percent of parents said their child had behavior problems or was in special schooling, and 39% said they had witnessed apneas. Using RDI greater than or equal to one as criteria for SDB, 63% of patients had SDB. There was no correlation between parental responses and objective data on PSG. The severity of the problem as predicted by parental report did not correlate with the objective severity demonstrated on PSG as determined by RDI and oxygen desaturation. Neither the mean nor median RDI, oxygen desaturation, sleep efficiency, percentage of REM sleep, and number of awakenings, differed between the parents who thought their child had a breathing problem and those who did not. There was no difference in the incidence of snoring between these two groups. There was no association between age, gender, or ethnicity and SDB.
Conclusion: Parental perception of their child's breathing problems during sleep is a poor predictor of objective sleep study findings. This realization has important implications regarding screening for SDB in children

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Cultural Influences on Bedtime Behavior of 3- to 6-year-old Children
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Introduction: Recent studies have revealed links between sleep hygiene and neurocognitive function in children. Parental education and belief structures may also affect responses to children's sleep patterns. Most epidemiological studies have focused on Caucasian populations and have failed to directly assess sleep behavior in other cultural or ethnic groups. The present study was designed to assess potential relationships of race and SES to bedtime behavior from a community sample of parents of 3- to 6-year-old children.
Methods: A previously validated sleep questionnaire was administered to parents of children enrolled in the Jefferson County, Kentucky school system. Sleep hygiene questions were answered in a scale ranging from "never" to "almost always." Due to few responses by other racial groups, only the sleep behavior of African American (n = 1,140) and Caucasian (n = 2,435) children was analyzed. Markers of SES included maternal education and zip code. Median annual income for each zip code was obtained from the U.S. Census Bureau. Logistic regression was utilized to determine the relationship of the independent variables of race, maternal education, and zip code with the dependent variables of sleep hygiene.
Results: Mean age was 4.77 ± 1.1 years. The majority of mothers had at least a high school education (Caucasian = 97%; African American = 95%). Caucasian families were significantly more likely to live in zip codes with median annual incomes greater than $40,000 (Caucasian = 88%; African American = 40%; $p < .001$) Mothers with less than a college education were more likely to reside in zip codes with median annual income below $40,000 ($p < .001$). African American children had later bedtimes than Caucasian children ($p < .001$) with similar rise times, resulting in significantly shorter sleep duration ($p < .001$), independent of SES. Caucasian children were reported to be more fearful at bedtime ($p < .001$) and to have more difficulty initiating sleep ($p < .001$) than African American children with no relationship to SES. Children residing in zip codes with annual median income below $20,000 were more likely to be "never easy to arouse" in the morning ($p < .05$) and to be unwilling to go to sleep at night ($p < .01$). Those residing in geographical areas with a median annual income above $40,000 were reported to be significantly more likely to "never or rarely fall asleep at school" ($p < .05$). Maternal education of high school or less was significantly associated with child unwillingness to go to sleep at night ($p < .001$).
Conclusion: Cultural variables impact bedtime behavior and sleep hygiene in children. Race, maternal education, and income have independent relationships with sleep hygiene. Independent of SES, while Caucasian children have more anxious symptoms prior to bedtime, African American children sleep less due to later bedtimes. SES does

play a role, however, in parentally-reported willingness to go to sleep and in the indicators of daytime sleepiness. Thus, cultural variables such as race and SES are important modifiers of reported sleep hygiene in children.

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A Comparison of the End-Tidal CO2 wave with the Nasal Pressure Transducer Tracing in Detecting Respiratory Events for the Diagnosis of Pediatric Obstructive Sleep Apnea

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Introduction: Recent pediatric polysomnogram guidelines recommend using end-tidal pCO2 (ETCO2) to detect obstructive hypoventilation. The nasal pressure transducer (NaPT) is touted as the most sensitive identifier of hypopneas in adults. Its use has also recently been described in children. Because both ETCO2 and NaPT are sampled by nasal cannula, use of both methods simultaneously is difficult. ETCO2's poor correlation with the apnea-hypopnea index (AHI) and it's inconsistent reflection of PaCO2 call into question the wisdom of using ETCO2 as an index of obstructive hypoventilation, especially if one must sacrifice other airflow measures (e.g., NaPT). In this study we compared the sensitivity of the CO2 waveform with the NaPT tracing in detecting airflow reductions.
Methods: We used a dual-lumen nasal cannula (BCI International Waukesha, Wisconsin) to simultaneously record both a CO2 waveform and NaPT tracing in 9 children who underwent full-night polysomnograms for suspected OSA. We did not employ any other inclusion or exclusion criteria. Two authors (SC, TC) scored by consensus the respiratory events. Respiratory events were scored using pediatric criteria first based on the CO2 wave while blinded to the NaPT tracing. The respiratory events were then re-scored using the NaPT tracing while blinded to the CO2 wave. Epochs in which one signal was lost were not scored in either run. Airflow reductions of 80% with ongoing effort and lasting 2 or more respiratory cycles were scored as obstructive apneas. Events lasting at least 10 seconds and without effort were scored as central apneas. Hypopneas were scored if any visible decrease in airflow amplitude occurred, which lasted at least 10 seconds and was followed by an EEG arousal or 3% oxygen desaturation.
Results: The subjects mean age was 7.25 +/-4.79 and BMI 22.01 +/-10.03. Total events scored with the CO2 /NaPT sensors were as follows: apneas: 25/203 and hypopneas: 14/325. The mean CO2 AHI (0.53 +/-0.51) was significantly less than the mean NaPT AHI (7.12 +/-1.44) ($p<0.001$). AHI did not strongly correlate with BMI ($r=-0.016$) or age ($r=0.075$). 10.8 % of the NaPT epochs and 1.4 % of the CO2 epochs were unscoreable. Every subject had a normal AHI based on the CO2 wave, but an abnormal AHI using the NaPT.
Conclusion: Because the NaPT identified more respiratory events (e.g., apneas and hypopneas) than the CO2 wave, we submit that it should be used in preference to the CO2 wave if only one can be used. We acknowledge that the CO2 wave signal is more robust (i.e., less prone to artifact) than the NaPT signal. However, a robust instrument that does not detect the parameter of interest (e.g., respiratory events) is not useful. We also realize that the NaPT does not detect ventilatory abnormalities such as elevated ETCO2. If one considers that ETCO2 correlates poorly with PaCO2 and, as we previously demonstrated, only identifies a few more cases of OSA than traditional measures of airflow (e.g., nasal thermistor), then there is little evidence to support the use of ETCO2 monitoring when it excludes the use of other measures of airflow.

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Relationships Between Sleep Variables and Neurocognitive Characteristics Suggest Differential Effects

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Introduction: A preponderance of research is mounting implicating the effects of sleep disordered breathing on neurocognitive functioning in children, more specifically, language, memory, attention, and visuospatial functioning. However, the differential effects of sleep on neurocognitive functioning in children are not well described. This study was therefore conducted to test the hypothesis that measures of REM sleep and oxygenation (as measured by pulse oximetry; SpO2) would relate to neurocognitive functioning differentially. It was predicted that as the apnea/hypopnea index (AHI)increased, specific scores on neurocognitive variables would decrease. Lower SpO2 and REM variables were expected to relate to lower performance on cognitive and behavioral indices.
Methods: Standard overnight multichannel polysomnographic evaluation and subsequent neurocognitive testing was conducted on 438 children between the ages of 5-7 years at the Sleep Medicine Center of Kosair Children's hospital. All children were recruited from the local community. The neurocognitive battery was administered the morning following the sleep study and included the Differential Abilities Scale (DAS), the NEPSY, the Conners' Parent Rating Scale, and the Child Behavior Checklist. Bivariate and partial correlation coefficients, and stepwise multiple regression analyses were conducted to examine the proposed relationships.
Results: As predicted, the AHI, SpO2 nadir, and the proportion of REM sleep (REM%) demonstrated unique differential associations with neurocognitive functioning. REM% was correlated with cognitive measures of attention, executive functioning, visuospatial relations as well as with behavioral measures of attention, hyperactivity and impulsivity. In contrast, on the cognitive measures, mild but significant relationships were found between AHI, SpO2 nadir and language scores. Verbal, Nonverbal and Composite scores of the DAS were related to AHI and SpO2 nadir in the predicted direction. In regard to the behavioral measures, as SpO2 levels decreased, anxiety, perfectionism and psychosomatic disturbance scores increased. Poorer visuospatial scores were related to all three of the sleep indices, as were verbal scores measured by the DAS. Using multivariant regression analyses SpO2 nadir and AHI accounted for approximately 30% of the total variance associated with language scores. SpO2 nadir accounted for approximately 29% of the variance associated with language scores while the addition of AHI did not add significantly to the prediction of the model. Conversely SpO2 nadir added stepwise to a model predicting language based on AHI scores and doubled the prediction of the model. Thus, lowest SpO2 reached appears to be a more robust predictor of cognitive and behavioral functioning in children than the AHI and it appears that the relationship between AHI and language scores is predominately accounted for by SpO2 levels.
Conclusion: We have found that disturbances in REM sleep as well as oxygen desaturations are correlated with both cognitive and behavior measures in a large cohort of children. These findings contribute to the growing body of literature implicating sleep disturbance and subsequent cognitive and behavioral deficits, and also demonstrate specificity of important sleep characteristics in relation to neurocognitive functions.

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Actigraphic Monitoring of Children With and Without Obstructive Sleep Apnea (OSA) During a Continuous Performance Task (CPT) Before and Following Sleep Restriction

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Introduction: Children with OSA have chronically disrupted sleep, which may cause deficits in cognition and attention regulation. The purpose of this study was to compare children with OSA and a comparison group on an objective measure of activity (actigraphy) during the Test of Variables of Attention (TOVA) to assess the impact of insufficient sleep on children's daytime functioning.
Methods: An actigraph (AMI) was worn on the non-dominant hand by 12 children during two neurobehavioral assessments; 5 subjects with OSA (3 boys, 2 girls, mean age: 8.2 SD=1.3) and 7 comparison group subjects (4 boys, 3 girls, mean age: 8.4 SD=2.0). The activity data, which consisted of movement intensity (PIM) was recorded in 1-minute epochs. Mean actigraph activity scores were calculated for the 22 minute TOVA sessions conducted in the mid-morning during weekend days. The TOVA is a standard computer-based CPT designed to assess sustained attention and the ability and response inhibition (impulsivity). The sleep restriction (SR) and baseline TOVA sessions occurred two weeks apart. Test time and environment were held relatively constant during the two sessions. Prior to the SR session subjects' sleep was restricted to 4 hours (sleep time 4-8am).
Results: The OSA subjects had a mean respiratory disturbance index of 12.18 (SD=20.86) and a nadir SaO2 of 87 (SD= 7.70). There was a trend for a time effect ($F(1,10)=3.58$, $p=.08$) and no group effect when TOVA activity levels were compared at baseline and sleep restriction. The OSA groups' activity level decreased 24% (baseline M=3273, SD=1735; OSA SR M=2294, SD=1284) while the comparison groups decreased 2.2% (baseline M=2219, SD=1309 and Comparison SR M=2126, SD=1430). A trend for a time by group interaction was observed in mean activity variability ($F(1,10)= 4.000$, $p=0.07$) when TOVA activity levels were compared at baseline and sleep restriction. The OSA group's mean variability decreased 50.6 % (baseline M= 1241, SD= 639; OSA SR 1040, SD= 530) while the comparison groups increased 14.47% (baseline M=1096, SD=582 and Comparison SR M=1374, SD=385). Significant group differences were observed for the TOVA d' statistic (a measure of target detection) $F(1,10)= 6.297$, $p= 0.031$ and a significant time effect was observed for the total omission errors ($F(1,10)= 5.950$, $p= 0.035$) on the TOVA. In addition trends for a group effect was observed for total omission errors, commission errors and correct response time variability ($F(1,10)= 3.63$, $p= 0.087$, $F(1,10)= 2.304$, $p= 0.160$ and, $F(1,10)= 2.984$, $p= 0.115$ respectively. These were all consistent with the hypothesis that OSA subjects performance was slower and poorer than that of comparison group.
Conclusion: Increased sleep disruption in OSA subject may contribute to their increased errors and poorer target detection on the TOVA. Trends for decreased activity and activity variability based on the actigraph may be another symptom of chronic and acute sleep disruption. These data suggest that there are group differences in cognitive performance in children diagnosed with OSAS and that fatigue caused by experimental sleep restriction and sleep disorders may manifest as overall slowing of activity and responsiveness.

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Neurobehavioral Assessment of the Effects of Sleep Restriction on Children with Obstructive Sleep Apnea OSA and a Healthy Comparison Group

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Introduction: OSA has been shown to impact children's neurobehavioral functioning. The specific mechanisms of the effects of OSA are not yet fully understood. In this study we used a neurobehavioral battery to understand the impact of chronic and acute sleep restriction on children aged 6 to 10.
Methods: To date 27 children, 16 in the OSA group (9 boys and 7 girls, mean age=8.5(sd=1.7)) and 10 in the comparison group (7 boys and 3 girls, mean age 8.5(sd=1.5) completed the protocol. All subjects completed a standard baseline PSG. Aside from OSA all subjects were healthy and free of psychiatric disorders. Subjects completed a baseline neurobehavioral battery on a weekend morning between 8:30am and 2:00pm. and then returned in exactly two weeks for the sleep restriction (SR) phase. Following a full day of wakefulness subjects were kept awake until 4:00am then slept till 8:00am. Subjects then completed a battery nearly identical to that conducted at baseline. The measures reported on here included, IQ (WASI-baseline and WISC-III Vocabulary at SR), a memory and response inhibition task (n-back paradigm) that paired targets with photos with positive, neutral and negative emotional valences, the emotional-face-go-no-go task, and the TOVA a standard continuous performance task.
Results: Differences were present in SES (parent education OSA<4 and comparison group>4 years of post secondary education and income, OSA=20-50,000 and comparison group=50-100,000) and the racial composition of groups (OSA- African American=14, caucasian=1, hispanic=1 and comparison group- African American=4, caucasian=4, other=2). Significant differences $t(24)=5.28$ ($p<.001$) were found at baseline on all IQ scales (full scale, OSA mean=92.4(sd=10.3) and comparison mean=111.9(sd=6.8)). Significant time and group effects were found on the vocabulary subtests from the WASI at baseline (OSA=8.3(sd=3.3), comparison=12.8(1.7)) and WISC at SR (OSA=7.4(sd=3.1), comparison=11.4(1.7)). On the affectively modified n-back task interesting trends suggested that on the easier 0-back portion, the comparison group tended be more sensitive to stronger emotional stimuli and on the 2-back portion, the OSA groups' reaction times slowed and accuracy decreased only minimally from baseline to. On the emotional-Face Go-No-Go both groups had increased omissions and decreased accuracy at SR compared to baseline while the comparison group's response time increased. On the TOVA, significant time ($F(1,21)=12.43$, $p<.003$)) and group ($F(1,21)$-5.12, $p<.001$) effects were found for omissions, and there was a group effect ($F(1,21)=4.18$) for reaction time. OSA subjects had greater performance decrements on the TOVA.
Conclusion: The OSAS subjects tended to have significant decrements in performance at baseline and to be significantly affected by SR. Verbal functioning and attention appeared to be most sensitive to the effects of chronic sleep disruption and acute sleep restriction. Comparison group subjects'increased errors may have been due to shorter reactions times suggesting greater impulsivity while the OSA group tended to be slower. It interesting to note that both groups' performance decreased on a standard IQ subtest (Vocabulary) that is assumed to remain stable over time. Differences in the racial and SES makeup of groups may account for some differences. It will also be important to explore the association between OSAS severity and performance.

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Prevalence Of Sleep Complaints And Insomnia In The Vitamins And Lifestyle (VITAL) Study Cohort Of 77,000 Older Men And Women

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Introduction: Introduction: Recent epidemiological studies have demonstrated strong associations between insomnia and health burden as well as hours of sleep and risk of mortality. Here, we report cross-sectional subjective sleep-related complaint data from the baseline assessment of the longitudinal Vitamins and Lifestyle (VITAL) Study.
Methods: Methods: Men and women were eligible to join the cohort if they were aged 50-76 and lived in the 13-county Western Washington State area covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry. A total of 364,418 survey questionnaires were mailed and a total of 76,660 (21.0%) eligible responses were obtained from 39,792 women and 36,868 men forming the cohort described below. Sleep-related complaints were reported as present at least half of the days of the previous year. This year-long duration of complaint is considerably longer than that typically used (e.g., two weeks, one month) when diagnosing insomnia.
Results: Results: 61.0% of the total cohort and significantly more women (64.1%) than men (57.6%) reported at least one of five sleep-related complaints. 17.6 % of the total sample reported problems falling asleep, 33.1% problems staying asleep and 26.6% problems waking up too early. 26.0% reported feeling unsatisfied or not rested and 13.3% feeling excessively sleepy during the daytime. Women were significantly more likely than men to report problems falling asleep, problems staying asleep, and feeling unsatisfied or not rested. When insomnia diagnostic criteria, defined as at least one of the three nighttime sleep complaints plus at least one of the two daytime sequelae, were applied; 21.1% of the cohort and significantly more women (23.6%) than men (18.3%) met criteria for insomnia. After accounting for gender, a significant negative relationship was found between insomnia and age. For example, 28.0% of women 50-55 yrs. but only 19.5% of women 70-76 yrs. met insomnia criteria. Examination of individual complaints revealed that while nighttime sleep complaints increased with age, complaints of daytime sequelae decreased much more strongly with age, resulting in an age-specific decrease in insomnia diagnosis. Similar, but not identical, age-related patterns of complaint were observed for men. The cohort's median reported time spent asleep was 7 hrs. 4.0% of the total cohort reported sleeping an average of five hours or less, 8.4% nine hours or more and 1.3% ten hours or more. Non-complainers were significantly more likely to be long sleepers (>9 hrs.), while insomniacs were significantly more likely to be short sleepers (<5 hrs.). All reported significances are $p < .0001$.
Conclusion: Conclusion: The prevalences of these sleep-related complaints and insomnia diagnoses, as well as the gender differences, observed in the VITAL cohort are comparable to rates published for other epidemiological samples of older adults (see Ohayon, Sleep Medicine Reviews 2002). The size of the VITAL cohort coupled with the study's longitudinal design, aimed at assessing mortality, will lend itself to prospectively addressing important questions of the inter-relationships among sleep, health and mortality.

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Relationship of Nocturia to Chronic Self-Reported Poor Sleep: Results from the 2003 NSF Sleep in America Poll

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Introduction: Nocturia (voluntary nocturnal voiding) is a common experience for many older adults but whether it is associated with chronically disturbed sleep remains uncertain, as most major epidemiologic studies have not examined its contribution. We assessed the relationship between nocturia and self-reported poor sleep and self-reported insomnia in the National Sleep Foundation 2003 Sleep in America Poll on Sleep and Aging.
Methods: Subjects were polled from a geographically-representative telephone random sample of telephone numbers for US households and were eligible if aged 55-84. Approximately 26% of eligible subjects (n = 1,506) completed the brief telephone interview (approx. 20-min) that collected data on sleep habits and health. Nocturia was defined as a response of every night or almost every night on a question regarding whether their sleep was disturbed by the need to get up to go to the bathroom. For this analysis, poor sleep was defined as rated quality of sleep as poor or fair on most nights. The presence of various medical diseases was defined based on a report of physician diagnosis for those conditions and concomitant treatment. Medical conditions examined included: heart disease, hypertension, arthritis, diabetes, cancer, stroke, pulmonary disease, depression, osteoporosis, enlarged prostate (men only) and memory problems. Analyses were based on those subjects with complete data (n = 1424).
Results: Nocturia was the most commonly endorsed reason for disturbed sleep in this sample (53%). Logistic regression analyses indicated that depression was the strongest predictor of self-reported poor sleep quality (OR = 2.56, 95% CI 1.68-3.90). Nocturia was the second strongest predictor (OR = 1.71, 95% CI 1.31-2.23). Other significant predictors included: osteoporosis (OR = 1.52, 95% CI 1.01- 2.30); arthritis (OR = 1.43, 95%CI 1.06-1.95) and female gender (OR = 1.35; 95% CI 1.02-1.79). Analyses employing self-reported insomnia (yes/no) showed a similar pattern of results. Nocturia represented a 75% increased risk of self-reported insomnia in this population, after controlling for the aforementioned co-morbidities. In the model for poor sleep quality, stratified analyses for men only including the diagnosis of prostatism did not affect the significance of nocturia.
Conclusion: These results suggest that awakenings to void, despite being ubiquitous, represent a common correlate of poor sleep in the US population, even when competing comorbidities have been taken into account. Although causal relationships (i.e., incidental voiding upon awakening vs awakening from a need to void) cannot be determined cross-sectionally, these data suggest that clinical trials treating insomnia should include nocturia as an outcome. Conversely, medication and behavioral trials modifying bladder function should also include sleep as a relevant outcome.

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Factors Associated with the Incidence and Remission of Difficulty Initiating Sleep in an Elderly Cohort-The Cardiovascular Health Study (CHS)

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Introduction: The elderly often report disturbed sleep. However, rates and risk factors for incidence and remission are not well studied. Also, data related to the importance of depression versus somatic factors to the development of poor sleep in the elderly are conflicting. Thus, we analyzed information pertaining to difficulty initiating sleep (DIS) obtained at the baseline (BL) and at a 1-4 year follow up (FU) examination of participants in CHS, a prospective multi-center study of cardiovascular disease (CVD) in elderly adults.

Methods: Data were analyzed from 4467 (41% men; mean age: 72.7 years; 82.9% White, 16.5% Black, 0.6% Other) of 5888 subjects in CHS who had answered a questionnaire item pertaining to DIS at BL and then at FU. Of the 1339 subjects excluded, 521 had died. All participants were >65 years of age at BL. The study design, methods of recruitment and demographics of the initial cohort have been published. Subjects were asked at both examinations, "Do you usually have trouble falling asleep?" On both occasions, responses were limited to "yes", "no", or "don't know". CVD was determined by electrocardiography, anti-anginal medication usage and medical record review. Depression was considered present if there was a score of >8 on the modified Center for Epidemiologic Studies Depression scale. Current medication use was coded using the National Drug Code. The occurrence of pulmonary symptoms, other medical problems and physical activity levels was assessed by questionnaire at both BL and FU.

Results: The annualized incidence and remission rates for DIS were 2.8% and 12.6% respectively. At BL, women were more likely to have DIS (75.3% vs. 24.7%, p<.0001). Men were less likely to develop DIS than women (OR=.53). However, there were no differences with respect to age or ethnicity. For men, use of hypertensive medications at BL and/or FU, impairment in activities of daily living at BL, and coronary heart disease (CHD) at FU were associated with incident DIS. For women, fair-poor self-reported health at BL and/or FU, BL arthritis and BL obesity (BMI >30) were related to the onset of DIS. For both genders, depression and use of psychoactive drugs at BL and /or FU were important risk factors for incident DIS. Men were less likely to have persistence of DIS (OR=.67). For women, depression at FU or both time points and the absence of respiratory symptoms at BL predicted persistent DIS. Factors associated with persistence in men were fair-poor self-reported general health at both FU and BL and the absence of CHD at BL. For both genders, use of psychoactive drugs at FU or at both time points were significant factors.

Conclusion: Depression, use of psychoactive drugs and female gender are the most important factors associated with the incidence and persistence of DIS in the elderly. However, in men, incidence of DIS also is related to the development of CHD and the presence of hypertension.

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Longitudinal Changes In Sleep And Psychosocial Function In Alzheimer's Patients And Family Caregivers

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Introduction: There is good evidence that sleep problems are associated with mood and functional disturbance in persons with Alzheimer's disease (AD), but the temporal progression of factors associated with the onset of sleep disturbances in AD is unknown. To address this gap, we have collected sleep data as part of a longitudinal study examining quality of life in AD.

Methods: Subjects were 231 AD patients living with their family caregivers. Caregiver and patient sleep reports were collected at baseline and every six months thereafter for the next five years. Caregiver sleep was considered to be disturbed if a Caregiver Sleep Questionnaire (CSQ) score was 12 points or higher, which was equal to the upper 25th percentile range for the sample at baseline. Patient sleep disturbance (PSD) was based upon the occurrence of two or more specific patient sleep behaviors including yelling, sleep-disordered breathing, hallucinations, agitation, "jerky" legs, and snoring. Waking the caregiver in the middle of the night three or more times a week was also considered indicative of patient sleep disturbance. Survival analyses were conducted to predict the onset of sleep disturbances in patients and caregivers over the five-year period. Patient cognitive and functional status, depression, behavioral disturbance, and caregiver depression and burden were considered as time-dependent covariates, using the score at the time of the event, the preceding visit (6 months earlier), and the change from the preceding visit to the current one. Caregiver and patient age and gender, and patient marital status were also evaluated. Hazard ratios [HR], with 95% confidence intervals are reported for 5-point differences, except for RMBPC-Depression, which is for one point.

Results: Measures of patient functional status, depression, and caregiver burden were the best predictors of longitudinal onset in sleep problems. An increase in current caregiver depression [CES-D; HR 1.47 (1.25, 1.73)] and subjective burden [SCB-subjective; HR 2.12 (1.42, 3.16)] at the previous visit were the most powerful predictors of a CSQ score of 12 or higher. A decrease in current activities of daily living [HR 1.34, (1.01, 1.77)], and increase in patient depression [RMBPC-Depression; HR 1.93, (1.37, 2.74)] best predicted a PDS score of 2 or greater. An increase in patient depression at the previous visit (HR = 2.04; 95% CI = 1.24, 3.37), current instrumental activities of daily living (HR = 2.24, 95% CI = 1.41, 3.55 for 5 points), and current caregiver CES-D (HR = 1.25, 95% CI = 1.05, 1.49) predicted frequent caregiver nighttime awakenings. Patient and caregiver demographics and overall patient behavioral disturbance were not significant predictors in the survival analysis.

Conclusion: Caregivers with increased depression were more likely to have sleep problems and more likely to complain about being awakened by their AD patient. A 5-point increase in subjective burden doubled caregiver risk of developing sleep problems six months later. Declining functional status was associated with development of patient sleep problems; patient depression increased risk for patient sleep problems both at the time of sampling and six months later.

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The Cardiopulmonary Response to Arousal is Diminished in Middle-Aged compared with Younger Men

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Introduction: Spontaneous arousal from sleep (È-α transition) is associated with an abrupt increase in cardiorespiratory output, as manifested by an increase in heart rate (HR), blood pressure and minute ventilation (Ve) to levels greater than subsequent stable wakefulness. While this "waking reflex" is thought to play a protective role in preparing the organism to interact with the environment, it may also have deleterious effects, as the hyperventilation seen with arousal could predispose to ventilatory instability and subsequent periodic breathing at sleep onset. The cardiovascular response could also precipitate acute coronary ischemia in a predisposed individual. There are currently minimal data on the effect of increasing age on the waking reflex in humans. We used nasal CPAP to eliminate upper airway resistance (UAR) differences between younger and middle-aged men during sleep such that we could examine the isolated effect of spontaneous arousals on cardiorespiratory parameters in healthy younger and middle-aged men.

Methods: We studied 12 younger (ages 18-25) and 11 middle-aged (45-65) healthy men. Subjects were studied while wearing nasal CPAP at 5-7cm H20 to minimize UAR during sleep. We measured breath by breath changes in Ve, UAR, epiglottic pressure (Pepi), genioglossal EMG (GGEMG), tensor palatini EMG (TPEMG) and diaphragm EMG (DIAEMG), along with beat to beat HR. Recurrent È-α transitions were identified by a previously validated computer algorithm and each breath was given a position prior to (–5 to –1) and after (+1 to +5) this transition. The È values for Ve, Pepi, and muscle activation were averaged over breaths –5 to –1, and the α values were then expressed as the % change from this pre-arousal mean value. We performed between group comparisons of the arousal effects on Ve, respiratory effort (Pepi), muscle activation and HR. In addition, we performed linear regression, correlating the changes in Ve with the changes in HR.

Results: As expected, nasal CPAP eliminated differences in UAR both during NREM sleep (1.62 +/- 0.3 vs. 1.59 +/- 0.4 cmH2O/l/s, old vs young) and after arousal. The ventilatory response to arousal was greater in the younger men as manifested as larger È-α related changes in Ve (18.0 +/- 3.2 vs. 10.6 +/-4.9 % increase, $p < 0.01$) epiglottic pressure (45.9 +/- 12.7 vs. 5.7 +/- 6.4 % increase, $p = 0.01$), DIAEMG (21.8% +/- 7.9 vs. 8.3 +/- 1.8 % increase, $p < 0.01$). No difference was seen in the increase in upper airway muscle activity with arousal (GGEMG, TPEMG, both p=NS). There was a trend for the peak change in HR to also be greater in the younger men (7.5+/-1.5 vs. 5.5+/-1.6 BPM, p=.14) at arousal. The change in HR at arousal was strongly correlated with the increase in ventilation ($r = 0.73$, $p<0.01$).

Conclusion: These data suggest that there is an age related decline in the magnitude of the waking reflex when measured under conditions of similar UAR. The fact that this difference did not extend to the upper airway muscles suggests that it is specific to the waking reflex, rather than a nonspecific manifestation of a lesser degree of arousal in the older men. The less robust ventilatory response to arousal in the older men would not be expected to destabilize ventilation, and suggests that this mechanism does not contribute to age related increase in sleep apnea prevalence. We speculate that the age related decrement in waking reflex may be due to the well known age-related decline in catecholamine receptors both centrally and peripherally. Furthermore, the correlation between the ventilatory and HR responses to arousal is consistent witht the hypothesis that the ventilatory response at arousal may drive the HR response.

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Insomnia and Hypnotic Use as Predictors of Falls and Hip Fractures in Older Nursing Home Residents

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Introduction: Insomnia and hypnotic use are common among older persons, and both are reported risk factors for falls and hip fractures. One prospective study of 70-75 year-old women found that hypnotic use, but not insomnia, independently predicted falls. However, previous studies often involved limited demographic groups, sample sizes, or covariates, and most did not use longitudinal assessments to establish whether risk factors preceded outcomes. We used a large, longitudinal database on Michigan nursing home residents aged 65+ to determine whether insomnia or hypnotic use after adjusting for other health conditions predict falls or hip fractures in the subsequent 6 months.

Methods: A baseline and a follow-up assessment were identified for each 2001 Michigan nursing home resident, from legally-mandated Minimum Data Set (MDS-2.0) records. Subjects were excluded if, at follow-up (150-210 days after baseline), they had died, been discharged, or no record was found. Assessors used all available information in completing the MDS. Logistic regression modeled any follow-up report of fall or hip fracture within 180 days of baseline. Predictors were baseline reports of recent insomnia ("insomnia/change in usual sleep pattern" during the past month), any use of hypnotic medication (past week), and several potential confounds including standard measures of functional status, cognitive status, intensity of resource utilization, proximity to death, burden of illness, number of medications taken, emergency room visits, nursing home new admission, age, and gender.

Results: For the 34,285 subjects (76% women) included in this analysis, the mean age was 84 ± 7.7 (s.d.) years. Insomnia predicted future falls before and after adjustment for all covariates (unadjusted OR = 1.90, 95% C.I. [1.74, 2.07]; adjusted OR = 1.51, [1.38, 1.66]). Hypnotic use predicted falls before, but not after, adjustment for covariates (unadjusted OR = 1.29, [1.13, 1.48]; adjusted OR = 1.13, [0.98, 1.30]). In comparison to subjects with no baseline insomnia or hypnotic use, insomniacs not treated with hypnotics at baseline were at increased adjusted risk for future falls (OR = 1.55, [1.41, 1.71]), as were insomniacs despite treatment with hypnotics (OR = 1.30, [1.01, 1.67]). However, hypnotic users without insomnia at baseline (suggesting effective treatment) were not at increased risk (OR = 1.11, [0.94, 1.31]). Insomnia predicted future hip fracture before adjustment (OR =1.45, [1.14, 1.85]) but not after (OR = 0.98, [0.77, 1.26]). Hypnotic use marginally predicted future hip fracture before adjustment (OR = 1.45, [1.01, 2.09]), but not after (OR = 0.84, [0.58, 1.22]).

Conclusion: This large longitudinal study suggests that insomnia but not hypnotic use predicts future falls in institutionalized older persons. Previous reports that hypnotics increase risk for falls may not have accounted for the large range of covariates included in this study. Furthermore, our findings suggest for the first time that successful amelioration of insomnia by hypnotics may protect against future falls. However, neither insomnia nor hypnotic use appears to be an independent risk factor for future hip fracture.

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Impaired Sleep Increases the Short-Term Risk of Mortality in Older Women: Preliminary Results from a Prospective Actigraphy Study

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Introduction: Previous large epidemiologic studies have reported associations between self-reported sleep and nap habits and risk of mortality. In particular, most studies have found that self-reported long sleepers (e.g. more than eight hours per night) and those reporting frequent or daily naps were at significantly higher risk of mortality as compared to those reporting more usual sleep patterns. However, our study is the first to examine the relationship between objective measures of sleep and nap habits, obtained using wrist actigraphy, and subsequent risk of death in older women, using data collected from the multi-center Study of Osteoporotic Fractures (SOF).
Methods: During the SOF baseline examination (1986-88), 9,704 women aged 65 and older were enrolled at four participating US clinic sites. The cohort was enhanced with an additional 662 African American participants aged ≥ 70 years approximately 10 years later. During an eighth round of clinic visits (Visit 8) beginning in 2001, sleep patterns were assessed by wrist actigraphy (SleepWatch-O®, Ambulatory Monitoring, Inc.) in 3,110 women aged 80 and older. Actigraphs were worn on the non-dominant wrist for an average of 4.1 nights (SD=0.82 nights). Deaths that occurred after Visit 8 (mean follow-up approximately 1.1 years) were ascertained by tri-annual contact with participants (if alive) or their next of kin, and confirmed using death certificates. Using logistic regression models, we determined the association between measures of sleep quality and short-term risk of mortality, after controlling for age, BMI, race, health status, comorbidities, depression, cognitive function, and use of sleep medications.
Results: Complete data on actigraphy and all covariates are available in 2,791 women, among whom 54 (1.9%) have died. Preliminary results suggest a U-shaped association between total sleep time and mortality: short sleepers (≤ 4 hours per night) were at 2.7 fold increased risk of death compared to those sleeping an average of 6-8 hours per night (Relative Risk=2.7; 95% CI=1.3 - 5.7); whereas long sleepers (> 8 hours per night) experienced a 2.6-fold increase in risk of death (RR=2.6; 1.0 - 6.6). Each 10% decrease in sleep efficiency (% of time in bed spend sleeping) was associated with a 21% increase in risk of mortality (RR=1.21; 1.07 - 1.38). The association between daytime napping and risk of mortality was more modest, indicating a 6% increase in risk of mortality per each additional 1 hour per week of napping (RR=1.06; 1.03 - 1.09).
Conclusion: Preliminary results from SOF indicate that older women with poor sleep quality are at significantly greater short-term risk of mortality as compared to those with more normal sleep patterns, even after accounting for potential contributing factors such as age, BMI, race, health status, comorbidities, depression, cognition, and use of sleep medications. Interestingly, both short and long sleep duration are associated with significantly higher risk of death. While further research is needed to elucidate the mechanisms for these associations, these preliminary results suggest that treatments to improve sleep quality in older women may enhance their survival.

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Characteristics of Objective and Subjective Sleep in Older Women: The Study of Osteoporotic Fractures (SOF)

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Introduction: The prevalence of sleep disorders increases with age and sleep disorders are increasingly recognized as contributing to poor health in the elderly. Previous studies have been limited by either self-reported measures or by small sample size. This is the first large prospective study of elderly community-dwelling women to assess correlates of sleep using both self-report data and wrist actigraphy.
Methods: The Study of Osteoporotic Fractures (SOF), is an ongoing prospective study of older women that enrolled 9704 community-dwelling ambulatory women aged ≥ 65 at 4 US clinical centers in 1986-1988 and enhanced the cohort with 662 African American women aged >70 approximately 10 years later. This analysis uses data from the eighth visit (Year 16) to characterize sleeping habits and correlates of sleep among women that completed a questionnaire (n=4404) and the subset of women that also completed wrist actigraphy (n=3110) with SleepWatch-O®. Actigraphy data include total sleep time (TST), sleep efficiency (% time in bed spent sleeping(SE)), long wake episodes (LWEP, number wake episodes >5 min duration), and total napping time (TNAP). Self-reported sleep and nap habits were obtained by questionnaire in the entire cohort, including the Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), and Epworth Sleepiness Scale (ESS). Using linear regression models, we examined the cross-sectional association between self-reported sleep habits and actigraphy data and a set of covariates, including age, race, medical conditions, cognitive function, and depression at Year 16.
Results: We found indications of significant subjective and objective sleep impairment in our cohort (mean age 84.1 years; 90% White). Actigraphy results indicate that 8% of women (n=251) slept ≥ 8 hrs per night, 18% slept <4 hours. 29% (n=889) had ≥ 80% SE and 32% had <60% SE. 30% (n=915) had ≥ LWEP per night and 29% (n=911) had <5. 8% (n=237) napped >2 hours per day and 46% (n=1420) nap <30 minutes per day. The mean TST was 5.7 hours (SD=1.9), mean SE was 66% (SD=20.2), 6.6 LWEP on average per evening (SD= 2.7), and an average of 48 minutes per day (SD=52) were spent napping. TST did not differ in women >90 years (referent <90) (p=0.61). There was a difference for LWEP (p=0.009), SE (p=0.003) and nap time (p=0.003) by age group, older women napped more, had poorer SE, and more LWEP. Self-reported data indicate that 4% (n=99) experience cessation of breathing during sleep, 1% (n=47) have been diagnosed with sleep apnea, 7% (n=285) diagnosed with a sleep disorder other than sleep apnea(146 insomnia, 172 restless leg syndrome (RLS)). 58% (n=1660) have ever snored, 88% (n=1463) of the snorers snore >=3 nights each week. The Mean ESS score was 5.7, 21% (N=927) suffer from excessive daytime sleepiness (ESS score >9). Mean PSQI score was 6.3, 51% were defined as poor sleepers (PSQI score >5) and mean FOSQ score was 15.3. The strongest determinants of sleep defined by both actigraphy and self-reported sleep habits overlapped and included age, BMI, exercise, anxiety, depression, cognitive function, heart conditions, and Alzheimers disease.
Conclusion: Many lifestyle factors and co-morbidities are associated

with both self-reported sleep and objective actigraphy data in community-dwelling older women. Our findings from both objective and subjective measures suggest a high prevalence of sleep disturbance among very elderly women. Actigraphy is useful in population studies of sleep in the elderly.

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Predicting Onset of Depression with Self-Reported Sleep Habits in Older Women

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Introduction: Previous studies have shown that sleep disturbances are independently associated with depression. Common complaints among patients with depression are that they have difficulty initiating and maintaining sleep and they do not feel refreshed in the morning. However, little research has been conducted on sleep disturbances and how they may predict future depressive symptoms in the elderly. In this analysis we examine whether self-reported sleep problems in non-depressed elderly women are associated with increased likelihood of developing depressive symptoms over time.
Methods: The Study of Osteoporotic Fractures (SOF), is an ongoing prospective study of older women that enrolled 9704 non-black, community-dwelling ambulatory women aged ≥ 65 at 4 US clinical centers in 1986-1988 and enhanced the cohort with 662 African American women aged >70 approximately 10 years later. In this analysis we used data from the sixth (Year 12) and eighth clinic visits (Year 16) of SOF (average time between visits=4.9 years) to evaluate the relationship between self-reported sleep habits and incident depression in 4269 women who completed a self-administered questionnaire at both visits. Poor sleepers at Year 12 were defined as those that had self-reported difficulty initiating and maintaining sleep or felt tired during the day due to unrestful sleep. Poor sleep at Year 16 was defined as scoring >5 on the Pittsburgh Sleep Quality Index. Depression status was determined at Year 12 and Year 16 visits using the Geriatric Depression Scale-15 point (GDS). Depression was defined as having scored >6 symptoms on the GDS. We excluded women who were depressed at Year 12 (n=336). Using logistic regression models, we examined the association between Year 12 self-reported sleep habits (i.e. trouble sleeping, awakening after sleep onset, daytime sleepiness, etc.) and risk of depression at Year 16. We adjusted our models for various medical conditions, lifestyle habits, and physical exam characteristics that were collected at Year 12.
Results: Among the 3933 women included in this analysis the mean age at Year 12 was 79.0 years. At Year 12, 34% of the women (n=1332) had difficulty initiating and/or maintaining sleep (DIMS) and 23% (n=880) felt tired during the day. 424 women (11%) developed depression (GDS>6) between Year 12 and Year 16. After adjustment for age, race, self-reported health status, several medical conditions, exercise, smoking, and cognitive impairment women reporting DIMS at Year 12 were more likely to report depressive symptoms at Year 16 (OR=1.98 (95% CI 1.58-2.49)). Similar results were seen in women that reported feeling tired at Year 12 after multivariate adjustment (OR=1.66 (95% CI 1.30-2.13)). Women that were depressed at Year 16 were also more likely than non-depressed women to report current problems sleeping on the PSQI (OR=2.02 (95% CI 1.63-2.49)).
Conclusion: We conclude that non-depressed older women with self-reported sleeping problems are at increased risk for developing depressive symptoms, even after adjusting for potential confounding factors for depression. Older women reporting difficulty sleeping or functioning due to poor sleep are at increased risk for depressive symptoms and should be targeted for depression screening.

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Nighttime NREM QEEG Energy Is Unrelated To Self-Endorsement Of Symptoms Of Disturbed Sleep In Non-Complaining Healthy Older Men And Women

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Introduction: The relationship between subjective and objective sleep quality is poorly understood. Previously we reported a significant gender difference in this relationship in a group of 150 healthy older adults who did not complain of significant sleep disturbance and who were carefully screened to exclude sleep disorders. We found a strong subjective/objective relationship for men (power ~ .75) but not for women. We concluded that what are typically considered objective measures of good sleep quality, such as sleep latency and efficiency, may be appropriate for older men but that older women may evaluate their sleep quality on other criteria. One such criterion may the NREM QEEG, specifically Beta and Gamma energy, which has been reported to be higher in insomniacs compared to control subjects. Here we examine the relationship between the NREM QEEG and subjective sleep quality in that same sample of 150 healthy older men and women.
Methods: We compared the baseline subjective (Pittsburgh Sleep Quality Index, PSQI) and objective (QEEG power spectral analysis, second of three recording nights) sleep of 150 healthy older (67.5+0.5) men (N=55) and women (N=95). QEEG variables included Delta (.5-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Sigma (12-16 Hz), Beta I (16-25 Hz), Beta II (25-35 Hz) and Gamma (35-45 Hz) energies averaged across all (artifact edited) NREM (stages 2, 3 and 4) epochs and normalized across 0.5-62 Hz.
Results: Despite their non-complaining status, significant proportions of women (33%) and men (16%) endorsed PSQI scores > 5, a criterion indicative of significant sleep disturbance. When examined as a function of this criterion, the QEEG was significantly different in the PSQI > 5 group with less Alpha (8.9+0.3 vs 7.7+0.4), Beta I (1.2+0.09 vs 1.0+0.06) and Beta II (1.3+0.2 vs 0.9+0.08) and more Gamma (0.3+0.08 vs 0.8+0.02) energy. However, comparable analyses for men, women and women as a function of estrogen replacement, revealed no differences of NREM QEEG energies as a function of PSQI status, indicating that the full subject group-based counter-intuitive finding was likely spurious and the result of large sample size, rather than representative of any underlying corresponding relationships within the sub-groups. A series of rank-order correlation analyses between QEEG variables and PSQI scores (ignoring the criterion cut-off) yielded comparable negative results.
Conclusion: These results fail to support an increase of NREM Beta and Gamma, or any other change in .5 to 45 Hz NREM QEEG energy, with increasing endorsement of symptoms of disturbed sleep either in healthy older non-complaining women (regardless of estrogen status) or in healthy older non-complaining men. Based on these and our previous findings, we conclude that polysomnographic measures of sleep quality such as sleep latency and efficiency, but not measures of the NREM QEEG, correspond with the PSQI-based subjective evaluations of sleep quality in older men, but that older women are judging their subjective

sleep quality on measures other than either polysomnographically assessed sleep or the NREM QEEG sleep measures examined here. The exact bases for the subjective evaluation of sleep quality in older women remain to be determined.

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Impaired Sleep Increases the Risk of Falls in Older Women: A Prospective Actigraphy Study

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Introduction: Falls are a major cause of fractures and disability in late life. Insomnia and other sleep disorders have been associated with decreased cognitive and physical function, both risk factors for falls. However, few previous studies have examined the relationship between sleep quality and risk of falls, and none have used objective measures of sleep. In a large cohort of older women participating in the multi-center Study of Osteoporotic Fractures (SOF), we tested the hypothesis that objective measures of sleep quality obtained using wrist actigraphy are associated with subsequent risk of falls.
Methods: During the SOF baseline examination (1986-88), 9,704 women aged 65 and older were enrolled at four participating US clinic sites. The cohort was enhanced with an additional 662 African American participants aged ≥ 70 years approximately 10 years later. During an eighth round of clinic visits (Visit 8) beginning in 2001, sleep patterns were ascertained by wrist actigraphy (SleepWatch-O®, Ambulatory Monitoring, Inc.) in 2,200 women aged 80 and older. Actigraphs were worn on the non-dominant wrist for an average of 4.1 nights (SD=0.82 nights). Analysis variables included average sleep efficiency (% of time in bed spent sleeping); long wake episodes (number of awakenings exceeding 5 min duration); and total hours slept during the night. Incident falls that occurred after Visit 8 were ascertained by postcard follow-up contacts every 4 months (self-report). 'Fallers' were defined as those who reported at least 1 fall per postcard interval during the follow-up period, which averaged 0.5 years. Using logistic regression models, we determined the association between measures of sleep quality and risk of being a faller, after controlling for age, BMI, race, comorbidities, depression, cognitive function, and use of sleep medications.
Results: 256 women (11.5%) were classified as fallers. In comparison with women having sleep efficiencies ≥ 80%, those with sleep efficiencies of <60% and 60-70% were significantly more likely to be fallers (Relative Risk=1.6; 95% CI 1.1 - 2.3 and RR=1.7; 1.1 - 2.6, respectively). Similarly, those experiencing more frequent long wake episodes were at increased risk of falling. Compared to women who slept 6-8 hours per night, women who slept fewer than 4 hours per night were 1.7 times more likely to suffer a fall (RR=1.7; 1.2 - 2.5), whereas those who slept 4-6 hours per night or > 8 hours per night were not at increased risk of falling.
Conclusion: Older women with objective evidence of sleep disruption (e.g. shorter sleep duration or more fragmented sleep) are at significantly greater risk of falling as compared to those with more normal sleep patterns, independent of other risk factors for falls. Improving sleep quality in older women may significantly reduce their risk of falling. This may have important implications in terms of fracture prevention and preservation of quality of life.

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Sleep and Cognitive Functioning in Elderly People with and without Insomnia

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Introduction: Chronic insomnia and cognitive impairment are both common complaints among older adults. Even so, only a few studies have examined the effects of chronic insomnia on cognitive functioning among the elderly, and the results of these studies are contradictory. We therefore examined whether insomnia is associated with changes in cognitive functioning among elderly people.
Methods: The study population comprised two groups: 63 elderly subjects without sleep disorders (mean age=71.6, SD=5.7; mean sleep efficiency=91.6%, SD=3.4), and 35 elderly insomniacs who exhibited actigraphically confirmed decreases in sleep efficiency (mean age=73.7, SD=5.7; mean sleep efficiency=74.5%, SD=8.9). All subjects were living independently in the community and were in good clinical condition. Participants completed the Mini Sleep Questionnaire (MSQ), the Mini-Mental State Examination and the Geriatric Depression Scale. None met any criteria for dementia or depression according to the Mini-Mental State Examination and the Geriatric Depression Scale. Subjects' sleep was continuously monitored for one week with a wrist actigraph (Ambulatory Monitoring, Inc.). The cognitive capacity of each subject was tested at the subject's home using the computerized "MindFit" test (CogniFit, Inc.). This enabled us to monitor cognitive performance and sleep objectively, under natural circumstances, and with minimal distortions. One of the major advantages of the "MindFit" test is that it was specially developed to provide a sensitive test for detecting reduction in cognitive functioning among elderly people, and it simultaneously provides several measures of cognitive functioning. Among these measures are: memory span, allocating attention to a target, selective attention, sustained attention, psychomotor skills, time estimation, executive functioning, and naming.
Results: Analysis revealed no significant differences between the insomniac and non-insomniac subjects in participant age [$t(96)=1.77$, $P>0.08$], consumption of sleeping pills [$\chi 2(6)=9.95$, $P>0.127$], and computer skills [$\chi 2(1)=1.75$, $P>0.186$]. A t-test for independent samples revealed significant differences between the insomniac and the non-insomniac subjects in memory span [$t(96)=2.124$, $P<0.036$] and executive functioning (working memory) tasks [$t(44)=2.283$, $P<0.027$]. Moreover, a two-way mixed design ANOVA revealed a significant effect on reaction time of sustained attention in tasks involving allocated attention to a target [$F(1, 379)=12.6$, $P<0.0001$], which was significantly longer for the insomniac participants compared to the non-insomniacs [$t(381)=3.56$, $P<0.0001$]. This preliminary analysis demonstrated that in three categories of cognitive functioning, elderly people with insomnia display significant impaired performance compared to non-insomniacs.
Conclusion: The results of this study highlight the associations between insomnia and cognitive functioning in the elderly. These findings suggest that insomnia may contribute to cognitive impairment in healthy older adults.

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Sleep Differences In Older African-Americans And Caucasians

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Introduction: This study explores differences in sleep between older African-Americans (AA) and Caucasians (C) at risk for sleep disordered breathing (SDB). We previously reported that after controlling for sleep apnea and leg kicks, although there were no differences in total sleep time (TST), AA woke up fewer times but had longer awakenings than C (i.e., greater wake after sleep onset; WASO). Here, in addition to the sleep disturbance variables, we controlled for health, exercise and socio-economic status variables (SES).

Methods: 70 AA men and women (mean age=73.69 years, SD=6.38, range =65-88) and 70 age and gender-matched C (mean age=73.27 years, SD=5.71, range =65-93) with complaints of loud snoring or excessive daytime sleepiness participated in the study. Sleep was recorded with the modified Respitrace/Medilog portable recording system (thoracic and abdominal respiration, tibialis EMG, and wrist actigraphy). TST, WASO, and number of wakes (Wakes) were measured, along with measures of sleep disturbance (apnea-hypopnea index -AHI, oxygen desaturation index -ODI, body mass index -BMI, and periodic leg movements in sleep -PLMSI). Multiple linear regressions were performed to investigate the relationship between race and TST, WASO and Wakes, controlling for sleep disturbance, health (medical burden: number of medical diagnoses received by participant; exercise: number of times participant exercised per week; walk scale: based on how far participant could walk; depression: GDS), and SES variables (income, highest school grade achieved, profession).

Results: There were still no differences found in TST between the races. When controlling for health and SES variables in addition to the sleep disturbance variables, the differences in WASO between the races were no longer significant. However, C woke up significantly more times during the night than AA (C mean wakes=53.90, SD=39.80; AA mean wakes =45.03, SD=29.23, p=.018) even after controlling for all the covariates.

Conclusion: This study suggests that, after controlling for sleep disorders, health and socio-economic status, the only difference in sleep between AA and C is in the number of awakenings with C waking up more often than AA. The reasons for this finding are presently unknown. Perhaps the inclusion of other variables in the model would help explain this difference.

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Relationship Of Regular Napping To Health And Self-Reported Sleep Quality In Older Adults: Results From The 2003 NSF Sleep In America Poll

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Introduction: Many epidemiological studies of sleep have reported that regular napping increases with advancing age, but few have reported on the association of regular napping with the co-morbidity of multiple chronic diseases, health behaviors and self-perceived sleep quality. We assessed these relationships using the 2003 National Sleep Foundation's Sleep in America Poll on Sleep and Aging.

Methods: Subjects were polled from geographically representative random samples of telephone listings for US households and were eligible if between 55 and 84 years of age. Approximately 26% of solicited subjects (n=1,506) participated in the brief telephone interview (about 20 minutes) that collected data on their sleep behaviors, medical conditions, sleep problems, and a few other socio-demographic and lifestyle attributes. 94% of respondents (n=1,417) answered all the questions in this analysis. Regular napping included those who reported napping 4 to 7 times a week. Co-morbidity was based on report of the following physician diagnoses with concomitant treatment: heart disease, hypertension, arthritis, diabetes, cancer, stroke, pulmonary disease, depression, osteoporosis, enlarged prostate (men only) and memory problems. Respondents also answered questions about age, sex, height, weight, hours of paid work per week, frequency of exercise, presence of bodily pain, symptoms of depression, sleep quality, self-defined insomnia and nocturia. Poor sleep was defined as self-rated quality of sleep reported as "poor" or "fair" on most nights.

Results: 14% of men and women age 55 to 84 reported regular napping, increasing with age from 9% (55 to 64 years) to 24% (75 to 84 years). Bivariate analyses revealed significant positive associations with number of chronic diseases, elevated BMI, bodily pain, symptoms of depression, fewer hours of paid work, nocturia, poor self-rated quality of sleep, difficulty maintaining sleep, and excessive daytime sleepiness (EDS). A multiple logistic regression model showed that in addition to increasing decades of age (OR=1.77, 95% CI=1.42, 2.20), regular napping was very strongly associated with EDS (OR=7.15, 95% CI=4.45-11.50) and with increasing medical co-morbidity (OR=1.22 per condition, 95% CI=1.07-1.39). In addition, persons who reported getting up every night to go to the bathroom (nocturia) were more likely to nap frequently (OR=1.43, 95% CI=1.01, 2.02). The other bivariate associations, including poor self-perceived sleep quality and other symptoms of insomnia, were explained by the effects of co-morbidity.

Conclusion: Regular napping increased with age and was significantly associated with EDS, medical co-morbidity and nocturia. Regular napping is likely a behavioral adaptation to EDS and/or inactivity related to poor health and possibly less work time. It is of interest that no other sleep quality measure (poor self-rated sleep, difficulty falling asleep, etc) was associated with napping after adjusting for medical co-morbidity, indicating that medical burden is highly associated with regular napping and accounts for all sleep complaints analyzed except for EDS. This suggests that EDS per se may lead to napping, perhaps as a result of lower daytime levels of arousal/wakefulness, rather than as a result of poor nighttime sleep. Additionally, nocturia, was also associated with napping, independent of EDS or co-morbidity, and may be an under-appreciated source of potential sleep disturbance and subsequent napping in community-dwelling older adults.

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The Association of Actigraphy Measures of Sleep and Cognitive Impairment in Elderly Women: The SOF Study

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Introduction: Several studies suggest there is an association between sleep parameters from polysomnography (PSG) and cognitive function. Whether sleep parameters from actigraphy are associated with cognitive function is less clear. Our analysis explores this relationship in 2988 elderly community dwelling women.
Methods: The Study of Osteoporotic Fractures (SOF) is a longitudinal study that enrolled 9704 Caucasian women from 1986 to 1988 and was enhanced by the addition 662 African American women in 1996. In 2002, 2988 women who returned for their bi-annual visit had data collected on both cognitive function and actigraphy. They were >=70 years old (mean age 83.5, SD=3.8) and 10.5% of the women were African American. The cutpoint of <26 on the Mini-Mental State Exam (MMSE, range 0-30) was used to define those with cognitive impairment. Actigraphy data was collected for an average of 4.13(SD=0.81) nights. The average over all nights was used to reduce variability. The actigraphy variables used were sleep efficiency, total hours slept at night, minutes of wake after sleep onset (WASO), and sleep latency. Total hours slept at night was categorized as <=4, 4 to 6, 6-8, and > 8 hours. Additional covariates including physical exam, health habits, and demographic data were collected. Logistic regression models were used to examine the association between sleep parameters and cognitive impairment. Models were adjusted for covariates that were associated to the outcome and predictor at the p=0.10 level.
Results: Overall, cognitive impairment occurred in 309 women (10.3%). For each standard deviation increase in sleep efficiency women had a 23% decrease in risk of cognitive impairment (odds ratio 0.77, 95% confidence interval 0.68-0.87). Compared to women with a total time slept at night of 6-8 hours per night, those who slept <=4 hours, 4-6 hours, and >8 hours were at increased risk of cognitive impairment (OR=1.59, 95% CI=1.11-2.28; OR=1.53, 95% CI=1.14-2.06; and OR=1.59, 95% CI=1.00-2.52 respectively). Women had a 9% increased risk of cognitive impairment for each 30 minute increase in WASO (OR=1.09, 95% CI=1.03-1.14). For each 1 hour increase in sleep latency women had a 1.23-fold increase in risk of cognitive impairment (OR=1.23 95% CI=1.11-1.36). All models were adjusted for age, race, functional status, body mass index, smoking and alcohol use, self-reported health, education, use of sleep medications, depression, and history of stroke.
Conclusion: Elderly women with poor sleep quality as defined by actigraphy have a higher risk of being cognitively impaired, even after adjustment for multiple covariates. Improvements in sleep in elderly women may decrease cognitive impairment. These results are for community dwelling elderly women, and may not apply to other populations.

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Micronized Progesterone Reduces MSLT Latency to Sleep Onset and Increases Subjective Sleepiness in Postmenopausal Women

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Introduction: Normal flucuations in endogenous progesterone levels (menstrual cycle, pregnancy) are associated with sleep changes. Also, some clinical reviews of hormone therapy recommend that postmenopausal women take progesterone in the evening to avoid unwanted daytime drowsiness. These data suggest that progesterone may influence sleep. However, little is known about the possible hypnotic action of progesterone. The purpose of this study was to determine the effects of micronized progesterone versus placebo on the sleepiness of postmenopausal women, as measured by a standard Multiple Sleep Latency Test (MSLT) and subjective self-report.
Methods: Nineteen healthy women aged 55-79 yrs (mean=66 yrs) participated in this double-blinded within-subjects study. All women were at least 5 years past menopause, not using hormones, and not having self-reported hot flashes. None had significant sleep complaints. PART 1: Subjects were given 300 mg oral micronized progesterone 1 hr after a controlled breakfast. Frequent blood samples determined the timing and size of the subsequent plasma progesterone peak. PART 2: After ≥ 1 week, subjects underwent two standard MSLT assessments, separated by 1-3 weeks. On the morning of each assessment, subjects took placebo or 300 mg oral micronized progesterone (counterbalanced order). The time between the medication and the beginning of the first MSLT nap trial was equal to the time required to reach the peak progesterone level for each subject, as measured in Part 1. (This time ranged from 60-180 minutes.) The second and third nap trials occurred 2 and 4 hrs later, respectively. Subjects rated their sleepiness just before each nap trial, using a standard Sleepiness Rating (scale of 1 to 9) and a Fatigue Scale (Lee, 1991).
Results: HORMONE LEVELS: Baseline progesterone levels were below assay sensitivity (<.2 ng/ml) for all women. After 300 mg progesterone, all women had significantly elevated progesterone levels, with a mean (± std dev) peak of 219 ± 194. The elapsed time to attain the peak averaged 112 ± 37 minutes. MSLT LATENCY: The average latency to sleep onset across the three nap trials was reduced by progesterone relative to placebo: 8.1 ± 5.0 minutes versus 9.6 ± 5.0 minutes (p<.05). On Nap Trial 1, when progesterone was at or near its peak plasma concentration, progesterone reduced sleep latency by an average of 29%: 7.7 ± 5.9 min (progesterone) versus 10.2 ± 4.9 min (placebo; p=.006). On Nap Trials 2 and 3, sleep latency remained lower following progesterone compared with placebo but these differences were not statistically significant. SUBJECTIVE SLEEPINESS: Subjects felt significantly more sleepy prior to Nap 1 in the progesterone condition compared with placebo, as indciated by a higher Sleepiness Rating score of 6.1 ± 2.1 versus 4.4 ± 2.4 (p=.000). The Fatigue Scale score was also significantly higher with progesterone: 46.3 ± 28.6 compared to 36.4 ± 24.3 (p=.016). SLEEPINESS-HORMONE RELATIONSHIPS: The peak progesterone concentration was not correlated with any measures of sleepiness or fatigue.
Conclusion: Oral micronized progesterone, taken during the day, increases objective and subjective daytime sleepiness in postmenopausal women. This 300 mg dose is equal to or somewhat higher than the doses prescribed for hormone replacement therapy. The results suggest that the very low postmenopausal levels of progesterone in women may have negative consequences for sleep. A study of progesterone effects on the nocturnal sleep of postmenopausal women is in progress.

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The Association of Subjective Measures of Sleep and Physical Function in Elderly Women: The Study of Osteoporotic Fractures

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Introduction: Little literature exists regarding the association between self-reported sleep habits and physical functioning in elderly women. This analysis explores this relationship in 6051 elderly community-dwelling women. We hypothesized that women with poor sleep habits would have decreased physical functioning.
Methods: The Study of Osteoporotic Fractures is a longitudinal study of 9704 Caucasian women that began in 1986 and was enhanced by the addition of 662 African American women 10 years later. At this sixth visit in 1996, 6051 women were evaluated and were asked about their sleep and nap habits. Physical function data included time to complete 5 chair stands, walking speed for a 6-meter course, and average grip strength. Reported total sleep time was categorized as ≤4, 4-6, 6-8 (reference group), and >8 hours per night. Women who answered often or almost always to one or more of the following questions were defined as having daytime sleepiness: feel unrested during the day, feel excessively sleepy during the day, do not get enough sleep. Linear regression and least squared means models were adjusted for covariates associated with the outcome (physical functioning) and predictor (subjective measures of sleep) at p=0.10. Models were adjusted for age, race, self-reported health, body mass index, exercise, smoking, alcohol use, history of cardiovascular disease/stroke, depression, cognitive impairment, and use of sleep medications.
Results: The mean age of these women was 79.9 years (SD=4.7), and 10.9% of the women were African American. On average, women who slept less took slightly less time to complete chair stands. Adjusted means were: ≤4 hours: 13.1 seconds, 95% CI=(12.1, 14.1); 4-6 hours: 13.3, 95% CI=(13.0, 13.6); 6-8 hours: 13.7, 95% CI=(13.5, 13.9); >8 hours: 14.6, 95% CI=(14.2, 15.0) (p-for-trend<0.0001). Compared to women who slept 6-8 hours per night, the only group that had significantly slower walking speeds were women who slept >8 hours (adjusted mean ± standard error (SE) = 0.83 ± 0.007 vs. 0.88 ± 0.003 m/sec, p<0.0001). The more the women slept, the weaker their grip strength - adjusted means were: ≤4 hours: 17.9 kg, 95% CI=(17.1, 18.6); 4-6 hours: 17.4, 95% CI=(17.1, 17.6); 6-8 hours: 17.1, 95% CI=(16.9, 17.2); >8 hours: 16.5, 95% CI=(16.2, 16.8) (p-for-trend<0.0001). Women who napped daily had slower chair stand times (adjusted mean ± SE =14.8 ± 0.22 vs. 13.6 ± 0.08 sec, p<0.0001), slower walking speeds (0.82 ± 0.008 vs. 0.89 ± 0.003 m/sec, p<0.0001), and weaker grip strength (16.4 ± 0.16 vs. 17.2 ± 0.06 kg, p<0.0001). Women with daytime sleepiness did not have significantly slower chair stand times (13.8 ± 0.15 vs. 13.6 ± 0.09 sec, p=0.41), but had slower walking speeds (0.87 ± 0.005 vs. 0.88 ± 0.003 m/sec, p=0.0099) and weaker grip strength (16.9 ± 0.11 vs. 17.1 ± 0.07 kg, p=0.0463).
Conclusion: On average, women reporting poorer sleep habits (longer nighttime sleep, daily napping, daytime sleepiness) have decreased physical functioning compared to women reporting better sleep habits. Future studies need to determine if poorer sleep habits are associated with an increased rate of decline in physical function.

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Usefulness of the PSQI Among Community-Residing Older Adults: Consideration of Ethnic Differences

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Introduction: The Pittsburgh Sleep Quality Index (PSQI) is a widely utilized measure of sleep quality. It differentiates between "good" and "poor" sleepers across a variety of populations including individuals with psychiatric, sleep, and somatic disorders, and it discriminates between individuals of varying agess and genders. It remains uncertain whether the PSQI is useful in discriminating among persons of different ethnicities. This study evaluated the usefulness of the PSQI in a community-based sample.
Methods: Volunteers (n = 64, age range = 60-85, Black = 59% and White 41%) were enrolled in a multifactorial study examining relationships between sociodemographic and circadian rhythm measures. Consented men (27%) and women (73%) provided subjective ratings of sleep quality, depressed moods, demographic, and health data. Additionally, they provided recordings of sleep and wakefulness for seven days (Actiwatch-L). Sleep quality was measured with the PSQI (α = 0.83). Depression was assessed with the Geriatric Depression Scale (GDS) (α = 0.79). Actigraphic data were scored with software provided by the manufacturer, aided by judgement of the score.
Results: Subjective sleep durations (SSD) and actigraphic sleep durations (ASD) were modestly correlated (r = 0.29, p < 0.01), and both showed acceptable night-to-night reliability (SSD: α = 0.80 and ASD: α = 0.85). Scores on the PSQI and the GDS were significantly correlated (r = 0.47, P < 0.01). Sixty-six percent of the volunteers were good sleepers and 34%, poor sleepers, with a mean global score of 4.66 ± 3.02. Both groups underestimated their SSD. While good sleepers reported an average SSD of 6.29hrs, ASD averaged 8.59hrs. Likewise, poor sleepers reported SSD averaging 6.17hrs, whereas ASD averaged 7.79hrs. Among good sleepers, ASD showed less variability (α = 0.87), relative to SSD (α = 0.79). Among poor sleepers, the converse was true: ASD were more variable (α = 0.75), compared to SSD (α = 0.81). Among Blacks, 71% of the volunteers were good sleepers, and 29% poor sleepers, whereas 59% of White volunteers were good sleepers, compared to 41% poor sleepers. Among Blacks, little discrepancy was noted in the night-to-night variability of ASD and SSD (mean = 8.35hrs, α = 0.84; mean = 6.22hrs, α = 0.82, respectively). However, among Whites ASD showed less variability (mean = 8.35hrs, α = 0.87), relative to SSD (mean = 6.52 hrs, α = 0.77).
Conclusion: As shown previously, sleep quality was predictive of depressed moods. Both good and poor sleepers showed the same level of variability in estimating their nocturnal sleep duration, and both under-

estimated their sleep durations. The tendency to underestimate one's sleep duration has been documented, but our data revealed that actigraphic sleep duration may be less variable among good sleepers. Unexpectedly, Blacks and Whites did not differ in terms of actigraphic or subjective sleep durations, although a greater percentage of Blacks were categorized as good sleepers, relative to their counterparts. This could not be explained by inconsistencies in their habitual sleep durations. Rather, Blacks may be experiencing sleep problems differently than do Whites.

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Detecting Sleep Apnea in Older Adults in the Primary Care Setting

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Introduction: Sleep apnea is generally under-detected in general practice. This may be particularly so for women. In a previous study we placed posters in medical waiting areas. The posters sought to recruit older individuals who are sleepy or fatigued during the day, and/or experience sleep problems at night. The ratio of men to women in this self-referred sample was 1:1.4. This is a very different referral rate from the 7:1 ratio often observed in sleep laboratories. These participants were found to be at high risk for sleep disorder. Furthermore, the ratio of men to women subsequently diagnosed with sleep apnea/hypopnea syndrome was 1.3:1. Men in our self-referred sample subsequently diagnosed with apnea generally endorsed the usual apnea-related signs on a questionnaire (e.g., daytime sleepiness, snoring). Women subsequently diagnosed with apnea also generally endorsed these apnea related signs. They, however, also endorsed numerous other items which indicated overall poor health satisfaction. Based on these data we hypothesized that the pattern of presenting symptoms in women might predispose the primary care physician to focus on medical aspects other than apnea. Thus, women's style of symptom presentation may be the basis for the dramatic under-referral of women for assessment in sleep laboratories. It was the objective of the present study to investigate possible male/female differences in presentation of apnea-related signs and symptoms in the medical setting directly.
Methods: Participants were 26 men and 30 women recruited from the waiting area of a large hospital-based family practice center. Consenting patients completed the Sleep Study Checklist immediately following their appointment with their general practitioner. This instrument, designed for the present study, contains a list of characteristic sleep apnea/hypopnea signs and symptoms (e.g. daytime sleepiness, snoring, waking with a dry mouth) embedded in a longer list of symptoms related to insomnia, daytime fatigue, psychological maladjustment, and health dissatisfaction. Respondents indicate whether they are experiencing each symptom currently, and whether the symptom was discussed with their physician at the current appointment or within the past year.
Results: Both men and women indicated many more symptoms that they were currently experiencing than those they had discussed with their physician at their current appointment or within the previous year. When symptoms were ranked in frequency, the hierarchy of experienced symptoms did not correspond to the hierarchy of symptoms presented to their physician, either for men or for women. The two most frequently presented symptoms were bodily pain and fatigue for both groups. Approximately 1/2 of the men and 1/4 of the women experienced some of the classic apnea-related signs and symptoms. About half of the male participants presented some of these to their physician (e.g., unwanted daytime sleep episodes). None of the women did so.
Conclusion: In this primary care setting, the ratio of men to women who experience apnea-related symptoms is approximately 2:1. However, women presented none of the symptoms which might direct a physician to investigate potential sleep disorder.

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Sleep During a Bedrest Extension Protocol in Older and Younger Individuals

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Introduction: As part of an investigation of homeostatic sleep and wake changes with aging, we studied sleep during increased bedrest opportunities in younger and older individuals.
Methods: Healthy older (target 60-80 years) and younger (target 18-30 years) men and women were studied. None were recruited by habitual bedrest duration (HBD). All were healthy by history, physical exam, EKG and laboratory tests of blood and urine and all passed a clinical sleep screen. None were using any prescription or non-prescription medications. Average data from 3 weeks of self-selected sleep-wake times were used to calculate the schedule for the week before admission. The actual sleep and wake times, as determined by self report and actigraphy, during that last week were used to schedule the timing and duration of the first nocturnal sleep episode (SP1) after admission to the inpatient portion of the protocol and to compute HBD. On the second inpatient day, subjects underwent 5 Multiple Sleep Latency Tests (MSLTs). For the next three days, the subjects were placed on a bedrest extension protocol with 16 hours of sleep opportunity: 12 hours centered at mid-habitual nocturnal sleep episode and 4 hours centered 12 hours opposite this. All sleep was polysomnographically recorded and scored according to standard criteria. T-tests were performed for differences between the age groups.
Results: HSD for 7 older subjects ranged from 7.0-8.9 hours; therefore we chose the 9 of the 17 younger subjects studied whose HSD was in the same range. During SP1, younger subjects had significantly higher amounts of NREM stage 4, REM sleep, Total Sleep Time (TST) and Sleep Efficiency; older subjects had significantly more Wake. During the MSLTs, all subjects fell asleep on all 5 MSLTS; there were no differences in the number of tests on which subjects fell asleep in < 5 minutes, or in the minimum, maximum or median sleep latencies. During the 3 days with 16-hr sleep opportunity, both younger and older subjects had declining average values of TST, SWS and REM sleep from day 1 -> day 2 -> day 3: TST 11.4 hr -> 9.1 hr -> 8.3 hr for older and 12.8 hr -> 11.1 hr -> 10.2 hr for younger subjects. All subjects had more TST during the first day of extended bedrest than during SP1. All younger subjects and all but one older subject had more SWS and more REM sleep during the first day of extended bedrest than during SP1. The younger subjects had more TST and more REM sleep on all three days, and more SWS on days 2 and 3 than older subjects.
Conclusion: These results suggest that both older and younger subjects will increase their sleep over their HBD when given the opportunity, though differences in TST between the age groups persist. The amount of increased sleep decreases progressively over days of increased sleep opportunity, suggesting recovery from a sleep debt. The increased sleep seen in older persons is less than that seen in younger, suggesting that older persons have less homeostatic pressure given the same bedrest history.

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Sleep Apnea in Geriatric Population

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Introduction: In a survey by the National Institute on aging of>9000 adults aged >65 years who were not in long term care, 42% reported symptoms of difficulty in both falling asleep and staying asleep. Causes of insomnia are thought to be multifactorial. The aging process itself is blamed too often. Sleep studies are usually deferred and patients are prescribed sedative hypnotics.
Methods: Eight patients aged 72 to 90 years of age were evaluated as office consultation.These patients lived in their own home. The mean age was 82.5 years.Five patients were males and three were females. Four patients presented with chief complaint of sleep maintenance insomnia. One patient had sleep initiation as well as sleep maintainance insomnia. One patient had daytime sleepiness. Two patients were seen for reasons unrelated to sleep disorder, although upon further questioning; their respective families agreed that they were excessively sleepy during the day. Only three patients had a history of snoring.The body mass index (BMI) ranged from 23 to 30. The mean BMI was 26.8 . Epworth sleepiness score (ESS) ranged from 0 to 10. Only one patient scored a 10. All others scored less than 7, with a mean ESS of 4.2 . In spite of an atypical history for sleep apnea, the patients were recommended to undergo a Polysomnogram (PSG) due to clinical suspicion for sleep apnea based on clinical exam and patient appearance.
Results: In six patients PSG revealed severe degree of sleep apnea;Respiratory Disturbance Index (RDI) > 40(Range 40.6 - 73.0). One patient had RDI of 31.2 and another one had RDI of 20.6. In 4 patients obstructive apnea index was >40(2 males and 2 females). Three patients had obsstructive hypopnea index >20 and one patient had obstructive hypopnea index of 17.4. All events were associated with moderate to severe degree of desaturations. Respiratory related arousals were>10/hr in 6 patients(range 12.2 to 31.2/hr).In 2 patients respiratory related arousals were <5/hr and both patients were taking prescription sedative hypnotic medications.
Conclusion: Geriatric population often does not present with typical history for sleep apnea. Sleep maintainance insomnia was the commonest presenting symptom. Patients were not aware of their degree of sleepiness during the day.Compared to younger population; the older population's severity of sleep apnea was worse in relationship to BMI.Geriatric population with sleep maintainace insomnia should be recommended to undergo PSG for evaluation of possible sleep apnea regardless of nonsuggestive history regarding sleep apnea.

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Rem Sleep And Behaviorally Observed Daytime Sleepiness In Demented Nursing Home Patients

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Introduction: Daytime sleepiness is common among nursing home (NH) residents, and probably determined by multiple factors. This study examined the relationship between the ratio of behavioral observations with sleep (OBS) during daytime hours to polysomnography (PSG) recorded on a subsequent night.
Methods: Forty-eight NH residents underwent sleep/wake observations every 15 minutes for 12 hours (0800-2000) for 5 consecutive days by trained research staff. Sleep was defined by eye closure and absence of gross body movement during 60 seconds of observation. OBS was defined as the ratio of sleep observations relative to the total observations for each patient. Demographic and clinical information, including the Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Charslon Comorbidity Index (CCI), were obtained from medical records and patient assessments. Overnight PSG was performed in each patient's room within 2 weeks of daytime observations.
Results: There were 37 female (77%) and 11 (23%) African-American subjects. Mean (±sd) age was 82.3 (±9.1), and 29 (60%) were taking one or more psychotropic medications. Mean (±sd) MMSE, GDS, CCI scores were 11.3 (±10.0), 4.5 (±2.7), 3.4 (±2.6), respectively. Mean (±sd) values for sleep efficiency, AHI, and REM% were 62.8 (±25.0) %, 17.3 (±21.7), and 12.8 (±8.5) respectively. OBS accounted for 19.2 (±14.6) % of observations (Range 0 % - 59.3%). Bivariate analyses showed statistically significant correlations between OBS and MMSE (rho -.489, P=.004), REM% (rho -.453. P=003) and a marginal association with CCI (rho .257, P=.082). RDI and sleep efficiency were unrelated to OBS (rho -.118 and -.108 respectively). Multiple linear regression with OBS as the dependent variable and age, MMSE, REM%, CCI, and number of psychotropics as independent variables indicated that only REM% was associated with OBS (Beta -.526, P = .001). After excluding subjects receiving psychotropics (n = 19), REM% remained a significant predictor (-.666, P=.009).
Conclusion: Our data suggest that greater levels of daytime sleepiness in NH residents may be related to reduced REM sleep at night. Previous studies have suggested that more severe dementia is associated with lower REM%. However, our results can also be viewed chronobiologically, to the extent that these data could be compatible with wake promoting function of an intact circadian timing system, apparently lost in severe dementing illness.

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The Effects Of 200 mg Of Caffeine On Spectral Analysis Of Sleep EEG In Young And Middle-Age Moderate Caffeine Consumers

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Introduction: It has been well demonstrated that caffeine induces prolonged sleep latency, reduced sleep efficiency, reduced slow wave sleep and increased awakenings during sleep in young subjects. Furthermore, reports have shown that caffeine produces a reduction in slow wave activity (SWA ; spectral power in 0.75-4.5 Hz), especially in the low oscillations (0.25-2 Hz), in the frontal, central and parietal cortical areas, accompanied by a rise in sigma spectral power (12.25-15 Hz) in central and parietal areas. Important modifications of the sleep-wake cycle appear between the ages of 20 and 60 years, which may render the middle-aged population particularly sensitive to sleep-wake cycle challenges. Yet, because this age-range population still has social and professional responsibilities, caffeine is widely used by middle-aged individuals to alleviate sleepiness. The aim of this study is to evaluate the effects of caffeine on spectral power and its topographical distribution in young and middle-aged subjects.
Methods: 22 healthy subjects, all moderate caffeine consumers (1-3

cups of coffee/day), were studied. They were separated into two groups according to their age; young (10 subjects, 20-30 y, 23.6 years (S.D. 2.2); 6W, 5M) and middle-aged (11 subjects, 40-60 y, 51.1 year (S.D. 4.9), 4 pre-menopausal W, 2 post-menopausal W, 5 M). All subjects were submitted to both caffeine (200 mg) and a placebo (200 mg of lactose) condition in a double blind cross over design, separated by one week. They received one capsule containing caffeine (100 mg) or placebo (100 mg) three hours prior to their habitual bedtime and the remaining dose (100 mg), one hour before bedtime. Power spectra (FFT, Cosine) were calculated on artefact-free 4-second epochs for frontal, central, parietal and occipital cortical areas. A three-way ANOVA, with one independent factor (Age) and two repeated measures (Condition and N-REM hour), for each topographic region was used.

Results: Compared to placebo, caffeine decreased delta power in all derivations ($p \leq 0.03$), and theta power in the central derivation ($p=0.02$) and alpha power in frontal and central derivations ($p<0.01$) in both age groups. While spectral power in low sigma (12.00-14.00 Hz) showed no condition effect, high sigma power (14.00-16.00 Hz) was increased in the frontal ($p=0.05$), central ($p=0.04$) and occipital ($p=0.04$) derivations following caffeine administration. Compared to placebo, beta spectral power (16.00-32.00 Hz) was enhanced after caffeine administration in the central derivation ($p<0.05$). A suppression of spectral power in the low delta (0.25-1.00 Hz) in the prefrontal region ($p<0.04$) and a rise in beta spectral power in the parietal region ($p=0.02$)following caffeine administration occurred solely in the middle-aged subjects, while no differences between caffeine and placebo were noticeable in the young.

Conclusion: Caffeine showed topographic and frequency specific effects in both age groups. However, very specific frequency bins were affected by the effects caffeine only in the middle-aged subjects. These subtle quantitative EEG results suggest increased sleep sensitivity to the effects of caffeine in the middle-aged subjects in spite of regular moderate caffeine consumption.

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Increased Brain Interconnectivity In Sleep: A Compensatory Effect?

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Introduction: The pre-frontal cortex (PFC), notably the left PFC, seems be vulnerable to both sleep deprivation (SD) and natural ageing. Brain imaging during SD indicates that the PFC recruits other non-specific brain regions (especially right parietal) to "help out". Given this background, we explore whether: i) sleep in healthy older people shows different patterns of inter-connectivity compared with younger people, ii) this inter-connectivity differs according to performance level at PFC oriented neuropsychological tests.

Methods: Eight young (range: 19-22y) and eight older (range: 61-70y) volunteers underwent two nights of sleep EEG recording and a series of these short, stimulating neuropsychological tests, mid morning All were healthy, normal sleepers without EDS or sleep disorders. The topography of interactions between cortical regions was investigated using analysis of non-linear synchronisation between four bipolar derivations (Fp1-F3; Fp2-F4; O1-P3; O2-P4). This analysis offers significant advantages over standard linear techniques (e.g. EEG coherence) in enabling strength and direction of interactions to be detected; thus attributing cause/effect. For each subject, 80-100, 1024 point epochs (sampling rate: 100Hz), during the first NREM period were analysed. Statistical analyses determined differences between non-linear/linear ratios and patterns of interactions in young versus old subjects, and subsequently good and bad test performers for the older group.

Results: No significant differences in the rates of non-linear interdependencies in each respective direction were found, thus subsequent findings were not due to underlying prevalence of non-linear interactions in one direction. However, there were significant differences ($p<0.05$) between the two subject groups in the topography of interactions, using the left frontal-to-right parietal derivation as a reference (i.e. during epochs when left frontal regions were 'communicating' with right parietal regions). Contrastingly, there were no such differences in the reverse direction, when the right parietal region 'communicated' with the left frontal region. The ratio of non-linear epochs, compared to all others, indicated that non-linear mechanisms were a key contributor to delta activity. Furthermore, this ratio analysis showed these non-linear contributions in the delta range to be larger in the older (~2.75:1) compared with the younger (~1.9:1) people. Neuropsychological test performance (older people) - The ratio of non-linearity in the left frontal-to-right parietal link (driving force of the delta rhythm?) was greater in 'bad' performers (~2.8:1) than 'good' performers (~1.8:1) at the tests. Similar ratios were found for the left-to-right frontal interaction, but not for any other interactions.

Conclusion: Using non-linear techniques, we find that during sleep with high delta activity, the left PFC is the dominant region, driving interactions between itself and right parietal areas. These interactions are stronger in older subjects, suggesting that the right parietal area is recruited to compensate for any age-associated decrements in PFC ability. This is supported by neuropsychological data where the 'worst' of the older subjects showed even greater communication between left frontal and right parietal regions.

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Effects of a Nap on Waking Function in Younger and Older Individuals

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Introduction: Older adults report obtaining insufficient sleep during the nighttime hours, probably related to physiological limitations on the amount of sleep they can acquire. Younger adults also report sleeping less than they would like. One result of this chronic sleep debt is decreased quality of life, particularly with respect to reductions in daytime functioning. It may be possible to fulfill the desired daily sleep "quota" by taking advantage of the robust biological tendency to nap at mid-day, near the circadian temperature maximum. Further, increasing 24-hour sleep amounts may be beneficial in terms of enhancing cognitive performance. The current study was designed to assess whether providing a strategically-placed nap opportunity would improve the waking function of individuals who do not, or cannot, obtain adequate sleep amounts during the normal nighttime sleep opportunity.

Methods: Twenty-six healthy young (Y: 17M, 9F; mean age = 35y; range 18-55y) and 32 healthy older (O: 16M, 16F; mean age 69y, range 55-85y) subjects without medical, psychiatric, or sleep disorders participated in two 3-day counterbalanced experimental sessions (Nap and

Sedentary). Subjects slept at habitual times and remained in the lab throughout the daytime hours. Training and practice on the computerized battery of performance tasks occurred on Night 1 and throughout the following day. On the day following Night 2, performance testing occurred at 0900, 1100, 1300, 1700, and 1900h. From 1400-1600h subjects either had an opportunity to nap (N) or remained awake and seated in a comfortable chair reading, watching TV or engaged in other sedentary activities (S). Performance was evaluated every 2 hours from 0900-1900h on the day following Night 3.
Results: All 58 subjects slept during the nap opportunity. The mean nap duration was 106±17 min for Y and 81±26 min for O. Both SWS and REM were observed in 85% (Y) and 72% (O) of the naps. There were no significant effects of napping on performance for the younger subjects. In contrast, in the older group, several performance measures were significantly enhanced in the nap vs. sedentary condition. Four Choice Reaction Time and Stroop Task throughput showed significant improvements ($p<0.03$, and $p<0.05$) in the hours immediately following the nap (ie, 1700h and 1900h). Next day performance was significantly improved on Stroop Task and Two-letter Search throughput, and Logical Reasoning accuracy. Subsequent nighttime sleep was in no way affected by the nap in the older group; analyses of sleep data in the young subjects are ongoing.
Conclusion: While a nap resulted in increased daytime performance in older people, a similar benefit was not observed in the younger group. One interpretation of these results is that older people require more sleep than typically obtained during the nighttime hours to achieve optimal waking function. On the contrary, younger individuals may desire more sleep but do not seem to need it to the same extent as older individuals. In conclusion, napping does not disrupt nighttime sleep, and may be an effective approach to alleviating deficits in waking function associated with age related truncation of nighttime sleep.

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Effects Of Acute Sleep Deprivation On Reaction Time And Inhibition Performances In A Stroop Task As A Function Of Age

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Introduction: The aim of this study was to assess aging and acute sleep deprivation effects on the efficiency of reaction time and inhibition in a Stroop task. Inhibition is an executive function that allows participants to ignore task-irrelevant stimuli in competitive trials between target and distractor. Many studies are consistent with a reduction in the effectiveness of the inhibitory processes in aging. Divergent findings relating to the sensitivity of executive functions to sleep deprivation in young adults appear and a controversy related to the sensitivity of elderly people to sleep deprivation on cognitive performances exist. Moreover, little is known about the effects of acute sleep deprivation on executive performances in older adults. Because of divergence or absence of findings, we decided to study the effects of aging and sleep deprivation on a Stroop task.
Methods: Twenty healthy male participants, 10 young (M = 22.5 years, SD = 2.17) and 10 middle-aged volunteers (M = 57.38 years, SD = 4.13) underwent evaluations to eliminate participants with sleep disorders. Elderly volunteers were given standard cognitive tests to screen people for abnormal deficits or evidence of dementia. Participants performed a Stroop Color-Word task. The participant was required to name the color of the ink in which strings of letters (control block) or color name word (incongruent block) were printed. So, the participant was required to inhibit word meaning. Response times per trial were recorded using a voice-key. The Stroop interference was calculated as an indicator of the efficiency to inhibit irrelevant information. Participants were tested in the laboratory after controlled usual sleep (rested condition) and after a full night of sleep deprivation (sleep deprived condition). One week was imposed between each condition in order to let the subjects rest.
Results: Analyses of variance (ANOVA) revealed an increase of reaction time and an impairment of inhibition performances in aging. Sleep deprivation did not affect inhibition performance for both groups. Moreover, analyses revealed an increase of reaction time in young participants when they are sleep deprived contrary to middle-aged participants. So, the results suggest a higher sensitivity of young people to acute sleep deprivation.
Conclusion: In conclusion, one night of total sleep deprivation did not affect inhibition performances in young and middle-aged people. Moreover, reaction times are more sensitive to acute sleep deprivation than inhibition function in young people. The present study provides evidence that the elderly suffer less from the adverse effects of acute sleep deprivation than the young. So, one night of total sleep deprivation does not seem to increase the deleterious effects of aging.

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The Effects of Aging on the Circadian Temperature Rhythm of F344 Rats

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Introduction: Satinoff and colleagues have shown that aged Long Evans (LE) rats are a heterogeneous population. By analyzing individual animal data, they have determined that some LE rats have sleep patterns and circadian Tb rhythms (CTRs) identical to those of young rats while other aged LE rats exhibit severely disrupted CTRs and sleep patterns. In this study, the CTRs of young and aged male F344 rats were studied to determine if this strain displays the disruptions reported in LE rats.
Methods: Twenty-four aged (22 mo) and 8 young (4 mo) male F344 were implanted with abdominal e-mitter transmitters for telemetry recordings of body temperature (Tb) and body movement. A subset of 12 old and 2 young rats were also implanted with EEG and EMG electrodes. Sleep recordings were conducted for 24 h under a 12h light/12 h dark cycle (LD 12:12) and again after 2 wk in constant dim red light (DD). Continuous Tb and LMA recordings were collected and stored on a PC using Vital View software and analyzed using ClockLab software. After 2 wk of baseline recording under LD 12:12, rats were released into constant dim red light (DD) to allow determination of the endogenous circadian period (τDD). Rats were then subjected to 15 min light pulses at either Circadian Time (CT)14 or CT22. After another 3 wk in DD to allow determination of the magnitude of the photic-induced phase-shift, animals were subjected to a second light pulse at either CT14 or CT22; the order of the two light pulses was counter-balanced among the rats. To confirm some effects of the first light pulse and to account for light pulse timing errors, a subset of 10 rats were subjected to a third light pulse 4 wk following the second light pulse. Three wk later, rats were placed into constant white light (LL) conditions for 3 wk to allow determination of the endogenous circadian period (τLL). Animals were then tested for re-entrainment to LD 12:12.
Results: Relatively small differences were found between young and old male F344 rats. Although the endogenous period of the circadian pacemaker was slightly shorter in aged rats in four separate determinations in

DD (τDD old=24.05 h; τDD young=24.07 h) and in one determination in LL (τLL old=25.00 h; τDD young=25.18 h), these differences did not reach statistical significance. On the other hand, the response to a 15 min phase-delaying light pulse delivered at CT14 was significantly reduced in old rats (-1.11 h) compared to young rats (-1.85 h) (p=0.006; t=3.24, df=15). The response to a 15 min phase-advancing light pulse delivered at CT22 did not differ between the two groups.
Conclusion: To this point, we have not found the remarkable changes in circadian system of the aged F344 rats that were described in the aged Long-Evans rat. Deterioration of the Tb rhythm was only evident in the last few weeks of life in almost all cases where death occurred spontaneously. Further analysis is required to investigate the possibility that more subtle changes distinguish different populations of aged F344 rats.

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Changes in Self-Reported Sleep Quality and Patterns Over Six Months in Older Adults (70+ Years)

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Introduction: Little is known about the variability of sleep quality and patterns in persons 70 years of age and older. Studies using younger samples (mean age: 65-70yrs), suggest that changes in sleep pattern are often accompanied by a change in health, mental status or daytime function. This paper examines changes in self-reported sleep quality and patterns over 6 months and their relationship to health, mental status, and daytime function in 54 community dwelling older adults (70+ years).
Methods: Fifty-four adults were studied (25M, mean age 77.9 years, 96% Caucasian). All exhibited a high level of physical, cognitive and emotional function at baseline: (mean: OARS Total=28; MMSE=29; Geriatric Depression Scale=1.0) and good health (mean: CIRS-G total=1.4; number of categories≥3= .22). The Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989) was administered at baseline and 6-month follow-up to obtain an overall measure of sleep quality and four measures of sleep pattern (sleep latency, sleep duration, sleep efficiency, types of sleep disturbances). Since both improvement and worsening of sleep patterns affect the quality of sleep, subjects were graded as having experienced a change if the absolute difference between baseline and 6 months met criteria for clinical significance: 3.4 points (1SD) in the PSQI. Changes in sleep patterns were defined as changes of: ≥ 15 minutes in sleep latency, ≥ 60 minutes in sleep duration, ≥ 10% in sleep efficiency, or the resolution or presence of any type of sleep disturbance. Improved sleep quality was defined as a decreased PSQI total score. Decreased sleep latency, increased sleep duration, or resolution of a sleep disturbance defined improvements in sleep pattern. Binomial tests assessed the probability that 5% or more of the sample had a change in sleep quality or pattern.
Results: Baseline sleep quality, sleep latency, duration, sleep efficiency, types of disturbances were consistent with previous reports. Sleep quality did not change significantly over the 6 months (p=.11 ns) but significant changes (p<.01) were observed in all four measures of sleep pattern. As a group, 11% reported no change in sleep pattern. Thirty-one percent reported an improvement (I) while 39% reported a decline (D) in at least one measure. Nineteen percent reported both an improvement and decline in one or more sleep pattern measure. Twenty four percent reported a change in sleep latency (I=11%, D=13%); 34% reported a change in duration (I=17%, D=17%); 34% reported a change in efficiency (I=11 and D=21), 72% reported a change in sleep disturbances (I=39, D=33). Increases in sleep latency and duration over the 6 months were associated with greater baseline impairments in baseline activities in daily living and severity of illness.
Conclusion: Sleep quality does not appear to change significantly over time, despite significant changes in sleep patterns in healthy, high functioning older adults. Further work is needed to understand the relationship between reported changes in sleep patterns, severity of illness, and daytime function in older adults.

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Differentiating 'Pathological' Delta From Healthy 'Physiological' Delta in Alzheimer's Disease

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Introduction: Sleep disturbances are a prominent and disabling feature of Alzheimer's disease (AD). In dementia, the EEG during wakefulness shows the pathological signs of abundant, diffuse large amplitude delta activity. This pathological slowing of EEG makes the distinction between sleep and wakefulness extremely challenging. More specifically, the 'carryover' of this abnormal delta activity during non-REM sleep makes it difficult to distinguish abnormal delta from normal physiological SWS delta activity. In traditional sleep studies of normal aging, SWS has been measured by observing spontaneous EEG over a full night's sleep. This observational approach is dependent on the sleep quality of the individual in the laboratory and precludes experimental manipulation of variables. In contrast to this traditional approach, we have devised an experimentally controlled procedure that measures the brain's ability to generate delta frequency EEG. The procedure involves recording single delta frequency events (K-complexes) in response to auditory stimuli, determining the probability of K-complex production and averaging the EEG responses to stimuli to produce sleep evoked potentials. Given that evoked K-complexes are a good surrogate of physiological delta in normal aging, we used the evoked K-complex methodology to measure physiological delta production in AD.
Methods: Participants included 8 ambulatory AD patients (mean age = 70.0 5.77 years) meeting the NINCDS and ADRDA criteria for probable Alzheimer's disease and 8 age-matched controls (mean age = 69.25 4.95 years). All participants underwent at least one night of evoked potential recordings. EEG was recorded from six gold plate electrodes (Fz, Fcz, Cz, Cpz, Pz and O2) referenced to A1 A2. Auditory stimuli were 80 dB, 1000Hz tone pips having 52 msec duration and a rise and fall time of 2 msec presented with a variable inter-stimulus interval (ISI) of 15 - 30 sec. Data were collected during stage 2 sleep. Responses to stimuli were classified based on whether they produced a K-complex which was defined as "a large amplitude waveform with a well delineated negative sharp wave, which was immediately followed by a positive component and which exceeded 0.5 seconds" or some other response not containing a K-complex.

Results: Independent samples t-tests revealed that the AD subjects produced significantly fewer evoked K-complexes (20 + 15 %) than the control subjects (51 + 13 %), $t(11) = 4.40$, $p = 0.001$. In addition, there was a significant difference between the two groups for N550 amplitude at Fz, with AD patients having substantially smaller amplitudes than controls, $t(14) = -3.21$, $p < 0.05$ but no difference between the two groups in terms of the N550 latency $t(14) = 1.17$, $p > 0.05$.
Conclusion: The present results indicate that it is possible to probe the sleeping nervous system and extract a delta frequency 'signal' in patients with AD. However, these subjects produce substantially fewer evoked K-complexes than age-matched controls and averaged evoked response waveforms in AD patients have a simplified structure and smaller component amplitudes than those observed in normal aging.

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Self-Treatment of Sleep Disorders in Older Adults

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Introduction: Sleep disorders are common in the elderly, with the prevalence rate for insomnia in particular ranging from 19-30% in this population. However, little is known about the different treatment options that elders elect to use. We conducted a study to determine the prevalence of the various types of treatments that older adults use for their insomnia and gauge their relative effectiveness based on self-report.
Methods: A 21-item questionnaire was developed which listed various treatment modalities for insomnia based on a review of the literature and interviews. Subjects were also asked to rate the relative effectiveness of that activity on a scale from 0 (not effective at all) to 4 (completely effective). It was mailed to a population-based cohort of older adults (age>65) living in the greater Philadelphia metropolitan area. Subjects with insomnia complaints were asked to fill out the questionnaire.
Results: 686 subjects were sent the questionnaire, of whom 460 responded (67% response rate). Of these 460, 247 (53.7%) complained of sleep difficulties and completed the treatment questionnaire. The most common treatment options were non-pharmacologic ones, including using the radio/TV or reading (59.1% and 52.6% respectively). Medications were also commonly used, with 35.6% taking pain medication, 27.1% using over the counter sleep aids, and 19.8% using prescription sleeping pills. Alcohol was used by 12.1% to help with their sleep. Vitamins or herbal supplements were used by 10.9%. Subjects used or had used an average of 4.7 different modalities (+/- 3.22), with 26.3% having used seven or more modalities in an effort to improve their sleep. Self-report of effectiveness was highest for prescription sleeping pills (2.18 +/- 1.31), with over-the-counter sleeping pills rated at 1.77 (+/-1.32) and pain medications at 1.71 (+/-1.17). Other strategies that were viewed as highly effective included reading (2.06 +/- 1.15) and using the radio/TV (1.84 +/- 0.97). When comparing treatment choices by gender, we noted that reading was preferred by women (63.9% of women vs 42.0% of men, chi-sq p=0.002). Patients who perceived their health as poor were more likely to take a pain medication (chi-sq p=0.005), use an over-the-counter sleeping pill (chi-sq p=0.02) or take a nap the following day (chi-sq p=0.06).
Conclusion: Our study has found that older adults engage in a variety of practices to help treat their sleep problems. Many of these practices center around non-pharmacologic interventions such as reading. Of the pharmacologic treatments, pain-relieving medications are the most commonly used; this is in accord with other research showing that pain is a common cause of insomnia. In general, elders felt that they received only moderate or little benefit from the different modalities. A significant proportion of elders used alcohol in an attempt to improve their sleep, a practice that in reality can worsen sleep quality and carries the risk of abuse. Our findings suggest that health care providers should ask detailed and direct questions regarding self-treatment of sleep problems as part of an evaluation of insomnia in order to counsel patients regarding potentially unhealthy activities.

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Evolution of PSG Sleep Parameters With Age

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Introduction: Sleep patterns in the context of the normal lifespan development are rather complex functions. Polysomnographic studies of sleep architecture have clearly demonstrated some sleep pattern changes: total sleep time, sleep efficiency and slow wave sleep all decrease with age while wake after sleep onset increases with age. However, some potential changes in sleep patterns remain less well defined. The purposes of this study were to identify age-related changes in objectively recorded sleep patterns across the aging process in healthy individuals using meta-analysis.
Methods: Literature was screen for research reports that investigated polysomnographic sleep parameters in healthy individuals aged 5 years or older. The research reports retained for the meta-analysis needed to fulfill the following criteria: 1) included non-clinical participants aged five years or older; 2) measures of sleep characteristics by PSG or actigraphy on one or more of the following variables: sleep latency (SL), sleep efficiency (SE), total sleep time (TST), stage 1, stage 2, slow wave sleep (SWS), REM, REM latency, and minutes awaken after sleep onset (WASO); 3) numeric presentation of the data; 4) articles published between 1960 and 2003 in peer-reviewed journals. These studies represented 2,600 subjects aged 5 years or older. Effect sizes were calculated and effects of seven moderators were also analyzed.
Results: In children and adolescents, Total sleep time and %SWS were significantly negatively correlated with age while percentage of stage 2 and %REM were positively related to age. Sleep latency and sleep efficiency did not change with age. Results on TST were modified by the method of recording (in-laboratory, ambulatory monitoring system or actigraphy) and by the time of the recordings (school days Vs. days off). In adults, total sleep time, sleep efficiency, %SWS, %REM sleep and REM latency were negatively correlated with age. Sleep latency, % stage 1, and WASO were increasing with age, as indicated by significant positive effect size values. The magnitudes of effect sizes changed depending on the researchers screened the participants for mental disorders, organic diseases, use of drug or alcohol, OSAS, or other sleep disorders.
Conclusion: Effect sizes for the different sleep parameters were greatly modified by the quality of the screening of the participants, diminishing or even masking the associations between different sleep parameter and age. From the meta-analysis, it appeared that the percentage of REM sleep decreased with age from childhood to old age but the decrease was not significant in individuals over 60 years. It also appears that the diminution in slow wave sleep that can already be observed from the

childhood went down steadily until old age. The number of studies that examine the evolution of sleep parameters with age are still scant especially among school-aged children and adolescents. There are also few studies that examined the effect of race on PSG sleep parameters.

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Effect Of Paradoxical Sleep Deprivation During The First Half Of Pregnancy On Cognitive Performance In Offspring

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Introduction: An early function of Paradoxical Sleep (PS) is to contribute to brain maturation. In the present study, we analyzed the effects of chronic PS deprivation (PSD) during pregnancy on learning performance of offspring in an hippocampus-dependant and a frontal-dependant spatial orientation memory task.
Methods: PSD was induced during the first 10 days of pregnancy in 10 Long-Evans rats, using the small platform method. Ten other pregnant females served as controls, using a large platform. Dams were individually exposed to the platform during the first four hours of the light period, starting at 8:00 AM, and then returned to their home cage. From day 11 of pregnancy on, rats remained in standard housing condition until delivery. Sixty-eight pups (30 PSD, 38 controls) were individually tested for six consecutive days, from post-natal day 21 to 27, in a water maze. Each of the six daily testing sessions consisted of four 40-second trials to locate and access a submerged escape platform. Half the pups were tested in the standard, hippocampus-dependant version of the Morris Water Maze: pups were started from a different quadrant on each of the four trials and had to rely on external visual cues to find the submerged escape platform. The rest of the pups were tested in an "alternation", frontal cortex-dependant version of the maze (Ethier et al., 2001): pups were always started from the same quadrant while the escape platform switched between two orthogonal positions. Cumulated time latency and number of quadrants entered before accessing the escape platform were measured. Testing days were averaged in pairs, where days 1-2 = adaptation period, days 3-4 = strategic elaboration, days 5-6 = long-term memory consolidation. Results were compared with T-tests for independent samples.
Results: In the alternation version of the water maze, PSD pups entered significantly more quadrants than control pups at days 3-4 (64.3±3.0 vs 51.9±3.0, $p < .05$). No differences were found on latency to access the escape platform. No significant differences were found between PSD and control pups for neither time latency or number of quadrants entered in the standard version of the Morris Water Maze.
Conclusion: Pups born from PSD mothers show difficulty elaborating a strategy in a frontal-dependant spatial orientation task. At least two possible sets of explanations can account for these results: 1) PSD interfered with in utero development of the substrates required to learn this task; 2) PSD had long-term effects on postnatal maternal-pup interactions, which lead to abnormal development of frontal cognitive abilities in the pups.

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Sleep and Sleepiness in First Year Medical Students

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Introduction: Although sleep deprivation during postgraduate medical training is a well-recognized problem, little is known about sleep in undergraduate medical students(1). Given the heavy academic workload, one would expect medical students to have sleep deprivation. The purpose of this study is to document the sleep/wake pattern and symptoms of sleep disorders in first year undergraduate medical students.
Methods: Eighty-four first year medical students attending the medical school at the University of Manitoba were given a modified version of a clinical questionnaire that is usually given to patients referred to our Sleep Disorders Centre. The students were asked to fill the answers voluntarily and anonymously.
Results: The medical students reported being in bed for an average of 7.1 ± 0.9 hours per night but they slept for only 6.77 ± 1.05 hours , which is somewhat less than the average hours of sleep for young adults between 7.4 to 8 hours (2-3). Twenty six percent of the Med I students reported being sleepy during the daytime, and 33% of them had an Epworth score of ten and above. Fourteen percent of the students napped daily and 78% had at least one nap per week. Average nap time was about one hour (63 ± 37 minutes). Symptoms consistent with restless leg syndrome (RLS) were described in about 27.5% of the study population. Eighty-two percent of the students used caffeine products. Their average caffeine intake was 2.2 cup/day (range 1-5). Thirty seven percent of the students did not consume any ethanol but among those who did, their average frequency was 1.6 times per week. Almost half of the students had donated blood (46%). Of those who donated blood: 40% donated five times or more; 21% donated ten times or more. A history of anemia was reported by 10% of all students. We were unable to establish a link between RLS and blood donation in this small group.
Conclusion: Medical students slept less than the average hours of night sleep and that resulted in increased daytime sleepiness and in many high Epworth scores. Most students napped. Whether the sleep deprivation and daytime sleepiness impacts their performance is unknown. Medical students frequently donated blood. Whether this has any effect on their having anemia or restless leg syndrome remains to be seen in future studies. References: 1. Gaba DM, Howard SK. Patient safety: fatigue among clinicians and the safety of patients. N Engl J Med. 2002;347:1249-55. 2. Williams R. EEG in Human Sleep. John Wiley and Sons. New York, 1974. p 51. 3. Acebo C, et al. Sleep, breathing, and cephalometrics in older children and young adults. Part I — Normative values. Chest. 1996;109:664-72.

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Homer1a mRNA Levels Increase During Sleep Loss

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Introduction: The regulation of synaptic efficacy is important for brain malleability. Hebbian plasticity is a form of positive feedback that strengthens effective synapses and weakens ineffective synapses. Unregulated Hebbian processes lead to instability and loss of synaptic diversity. Synaptic scaling is a mechanism whereby an increase in network activity causes a slow compensatory decrease in efficacy of excitatory synapses, and a decrease in network activity increases excitatory synaptic strength. The Krueger-Obal theory of sleep (function and brain organization) posits that mechanisms, driven by sleep regulatory substances, are responsible for sleep/wake state transitions and give rise to an essential function of sleep by preserving synaptic diversity. Homer1a is an activity-dependent protein that could play a role in synaptic scaling by weakening the interactions of the other members of this gene family (Homer1b, c 2,3) in the synapse. Homer proteins 1b, 1c, 2, and 3 interact with each other to hold various target proteins in close proximity. These Homer proteins couple metabotropic glutamate receptors 1 and 5a to IP3 receptors and regulate the availability of class I metabotropic receptors. Homer1a interrupts these interactions because it lacks the coiled-coil domain necessary for multimerization. Thus Homer1a decouples systems in which Homer proteins are involved. We therefore determined the effects of sleep loss on Homer 1a expression.
Methods: Four groups (n=10) of rats were used: Control, unilateral whisker cut (WC), sleep deprived (SD), and SD+WC. Animals were on

a 12/12 light cycle with lights on at 4:00am and acclimated to WC procedure by holding a razor near whiskers 5 min/day for 3 days. WCs were at 4:00 am. The rat unilateral WC is a plasticity model because after the WC, input to the barrel fields changes on both sides. SD was by gentle handling for 6 hours. Animals were sacrificed under halothane anesthesia by decapitation, 10:00 to 11:00am. Brains were blocked then preserved in RNAlater. The barrel fields were dissected and total RNA prepared using Trizol. Real-time PCR was performed using 7.5 ng cDNA and UDG supermix. All samples were run in triplicate; the average Ct value for cyclophilin was subtracted from the average Ct value for Homer1a to determine ΔCt for each sample. Differences between populations were calculated by the formula ΔΔCt= ΔCt control -ΔCttreated. Fold Change=2ΔΔCt

Results: WC enhanced Homer1a expression by 2.3 fold on the contralateral side (p=.002) and 3.7 fold on the ipsilateral side (p=0.000002) relative to intact animals. SD increased Homer1a expression by 5.5 fold (p<0.000001). WC+SD increased Homer 1a expression by 19.6 fold (p<0.0000001) relative to non-sleep deprived non-whisker cut control on both sides.

Conclusion: The increases in Homer1a mRNA expression after WC, SD and WC+SD support the hypothesis that Homer1a plays an activity-dependent role in synaptic scaling and thus, is a candidate for the synaptic stabilizing influences of sleep.

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Sleep In Prolactin Deficient Mice: Effect Of Sleep Deprivation And Prolactin Replacement

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Introduction: Systemic or intracerebral administration of exogenous prolactin (PRL) to rabbits or rats enhances duration of REMS and hyperprolactinemic rats display more REMS. Furthermore, antibodies to PRL reduce spontaneous and block VIP-enhanced REMS in rats. Mice with targeted disruption of the PRL gene provide an excellent tool to study the role of PRL in REMS regulation. The objectives of this study were to characterize sleep patterns in PRL deficient (PRL-/-) mice and to understand role of PRL in REMS rebound after sleep deprivation. We also determined the REMS response to PRL replacement in the PRL-/- mice.

Methods: Heterozygous (PRL+/-) and homozygous males (PRL -/-) were used. The (PRL-/-) animals secrete a truncated PRL that has no known biological activities whereas the PRL+/- animals produce PRL of normal size, activity, and quantity. EEG and EMG were recorded. Starting at light onset, the mice (n = 10 for PRL+/- and n = 10 for PRL-/- mice) were recorded from for 2 consecutive days to obtain baseline values of spontaneous sleep/wake activity. On the third experimental day the mice (n = 6) were deprived of sleep (SD) by gentle handling (6 hours) beginning at light onset. The mice that were used in the PRL replacement experiment (PRL-/- n=10) were subcutaneously implanted with osmotic minipumps (ALZET, 0.25 μl/h for 14 days). The minipumps were filled with recombinant murine PRL (AFP-306C) (from Dr. A. F. Parlow, Harbor-UCLA REI) in physiological saline delivering 4.26 μg PRL/day. A group of PRL+/- mice (n=10) received saline-loaded osmotic pumps. Spontaneous sleep-wake activity of the minipump-implanted mice was recorded on days 12 and 13 of the PRL or saline infusions.

Results: Time spent in NREMS did not change in the PRL-/- mice compared to the PRL+/- mice. Time spent in REMS was significantly lower in PRL-/- mice compared to PRL+/- mice. (PRL+/- 62.74 ± 6.67 min vs. PRL-/- 40.70 ± 7.50 min, F = 15.43, P < 0.001). The duration of REMS episodes was longer in PRL+/- mice than in PRL-/- mice during the day (PRL+/- 1.30 ± 0.04 min vs. PRL-/- 1.15 ± 0.05 min, F = 12.33, P < 0.001). After SD, REMS was less in the PRL-/- mice than in the PRL+/- mice (p<0.05), thus time in REMS remained decreased after SD in PRL-/- mice. Compared to PRL+/- mice there was a decrease in the frequency of REMS episodes during the dark period (PRL+/- 21.12 ± 2.82 vs. PRL-/- 7.29 ± 1.96, F = 27.79, P < 0.001). PRL replacement restored duration of REMS in PRL-/- mice to that observed in PRL+/- mice.

Conclusion: Results provide additional support for the hypothesis that PRL is involved in physiological REMS regulation.

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Sleep Restriction Increases IL-6 Levels And Pain-Related Symptoms In Healthy Volunteers

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Introduction: Chronic under-sleeping and chronic pain are both highly prevalent complaints in our society, but little is known about their possible interrelationship. Beside classical inflammatory markers, such as prostaglandins (PGs), there is increasing evidence that cytokines, in particular interleukin 6 (IL-6) are involved in pain processing, probably by sensitising primary sensory neurons. We hypothesize that chronic sleep restriction lowers the pain threshold, and that this is associated with increased basal levels of inflammatory markers.

Methods: Forty healthy young subjects who normally slept between 7-9h/night were studied under controlled in-lab conditions of "normal sleep" (n=18) or "sleep restriction" to 4 hours per night (n=22) for 10 consecutive days. In the normal sleep condition, subjects slept from 2300 to 0700h. In the sleep restriction condition, subjects slept from 2300 to 0300h, and stayed awake in bed in a semi-supine position until 0700h. All subjects were closely monitored by an experimenter throughout the waking periods of the study to prevent any non-scheduled sleep episodes. In addition to cognitive performance testing, subjects estimated the presence and intensity of mood states and of pain-related symptoms on computerized visual analogue scales every 2 hours throughout the scheduled waking periods. At the baseline day and the 10th experimental day, urine was collected, and blood was sampled across 24 hours through an intravenous catheter. In seventeen subjects (n=9 in the sleep restriction group, n=8 in the normal sleep group), IL-6 was measured in plasma, and PG metabolites D2 and E2 were measured in urine.

Results: While subjects sleeping 8 hours per night showed constant levels, sleep-restricted subjects showed a significant increase in ratings of fatigue within the first 3 days (p<0.05), and overall emotional and cognitive well-being gradually decreased, with ratings of items: grouchy, unfriendly, upset, unmotivated, effort to do anything, unable to concentrate, confused, all showing increases (p<0.05). The occurrence of headache, backache, stomach pain, generalized body pain, and physical discomfort increased across days of sleep restriction (p<0.05), whereas subjects sleeping 8 hours per night maintained stable levels of pain-related estimates. Urinary PG metabolites D2 and E2 slightly, but not significantly increased to a greater extend from baseline to the 10th experimental day in the sleep restriction group compared to the normal sleep group. Plasma levels of IL-6 increased on average about 75% (equivalent to 1.5 pg/ml) from the baseline day to the 10th experimental day in the sleep restriction group, whereas IL-6 levels decreased in the normal

sleep group ($p<0.05$ for group by day interaction effect). In all subjects, changes in IL-6 levels from baseline to the 10th day were positively correlated with changes in estimations of fatigue ($r=0.57$, $p<0.05$) and pain-related symptoms (r between 0.42 and 0.54, p between <0.05 and <0.10).
Conclusion: These data provide support for the hypothesis that chronic under-sleeping contributes to the high prevalence of pain experienced in the general population. Furthermore, these data demonstrate that 10 days of sleep restriction leads to a mild elevation in IL-6 levels, an important inflammatory modulator, and this increase may contribute to the experience of fatigue and the sleep loss-pain relationship we observed in the present study.

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Verbal Learning Performance Following 36 Hours of Total Sleep Deprivation in Long and Short Sleepers

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Introduction: Research groups have recently utilized naturally long (LS) and short (SS) sleepers as a paradigm to better understand sleep and sleep deprivation. However there are no published reports of cognitive performance following total sleep deprivation (TSD) in these groups. It is unknown whether large individual differences in habitual sleep length influence vulnerability to TSD. In an effort to better explain this dynamic, this study examined verbal learning performance in LS and SS during TSD.
Methods: Five LS (22.2, ±4.6 years, 4F) and six SS (38.8, ±12.2, 2F) were recruited through local media. Of approximately 1000 people screened, 14 subjects met full eligibility criteria and participated in the experimental portion of the study. Subjects spent four nights in the lab over a 2-3 week period, including an Adaptation Night (AN), a Normal Night of sleep (NN), 36 hours TSD, and a recovery night (RN) of sleep. NN and TSD were counterbalanced across subjects within group. After an initial practice session, subjects performed a verbal learning test four times: 36 hours into TSD, 2 hours after waking from RN, and 2 and 12 hours after waking from NN (which correspond to the same times of day as the other two sessions). Following each session, immediate free recall was tested and subjective assessments were obtained using Likert scales for five different indicators (task difficulty, effort required, effort invested, concentration, and motivation). Delayed free recall and recognition memory was also tested.
Results: Average bed and wake times (based on 2 weeks of actigraphy) were 00:05 (±0:44) and 09:14 (±1:00) for LS and 00:53 (±0:58) and 06:38 (±1:00) for SS. Mean sleep duration was 546.9 ±23.6 minutes for LS and 344.2 ±31.6 minutes for SS, with no significant differences in sleep efficiency (LS = 90.8 ±6.6%, SS = 90.3 ±5.8%). Based on 5 neuropsychological tests given during screening, as well as the practice verbal learning test, there were no baseline cognitive performance differences between LS and SS. LS did not show any significant differences in performance between NN, TSD, RN. SS, on the other hand, performed significantly worse on immediate recall, delayed recall, and recognition after 36 hours TSD compared to both NN and RN. No significant differences were found between the SS and LS at any testing session on pretest Stanford or Karolinska Sleepiness Scales nor any subjective measurement posttest.
Conclusion: Individual differences in habitual sleep length appear to influence the response to TSD during performance of a verbal learning task. SS perform at the same level as LS while well-rested, but unlike LS, SS show a significant decrement in verbal learning after 36 hours TSD. SS recover fully, however, after one night of recovery sleep. These data suggest that LS seem to be more resilient to sleep loss, at least with respect to verbal learning. Habitual sleep need, therefore, may be an individual difference variable that can predict response to TSD.

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Oculomotor Measures Over 30-Hours of Continuous Wake With and Without Caffeine

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Introduction: Variation of saccadic velocity and components of the pupillary light reflex have been shown with extended wakefulness in partial chronic sleep deprivation. The present study assessed for oculometric changes in military volunteers over 30 hours of continuous wake with and without caffeine in order to assess the combined effects on oculometric measures of extended wake and a commonly used fatigue countermeasure.
Methods: Saccadic Velocity (SV), Initial Pupil Diameter (IPD), Latency to Pupil Constriction (LPC), and Amplitude of Pupil Constriction (APC) were tested in 21 volunteers (20m/1f, 18-41yrs, mean 26.5 +- 7.1 yrs) using the FIT 2003 oculometer (Pulse Medical Instruments, Rockville, Maryland) in a double-blind, placebo-controlled, cross-over extended wake caffeine chewing-gum experiment. A control period on day one was composed of 16-hours waking (0700-2300) followed by 8-hours time-in-bed. A 30-hour continuous wake period began at 0700 on day two. Caffeine or placebo was administrated on day two at 2130 (400mg, gum), and on day three at 0300 and 0500 (100mg, gum). Oculometric measures were collected pre-dosing at 0800, 1000, 1200, 1500, 1730, 2100 and post-dosing at 0230, 0400, 0630, 0830, and 1030. Comparisons are to the 0800 control day baseline value. The differences over time between the baseline and every other session were tested individually for the caffeine and placebo groups by Paired t-tests with Bonferroni corrections. Group differences were analyzed for each session using Paired t-tests with Bonferroni corrections. Preliminary analyses are presented.
Results: 1. Saccadic Velocity decreased in placebo group at 0230, 0400, 0630, 0830 ($P<0.0033$, d.f.=20) and in caffeine group at 0230, 0830 and 1030 ($P<0.0033$, d.f.=20). No significant differences were found between placebo and caffeine groups, although SV was faster in the caffeine group than in placebo group at 0400, 0630 and 1030. 2. Initial Pupil Diameter increased significantly in the placebo group at 0230 ($P<0.0033$, d.f.=20), while in the caffeine group did not change significantly. IPD between caffeine and placebo groups was not significant at any tested time. 3. Constriction Latency in the placebo group increased significantly at 0400 ($P<0.0033$, d.f.=20) but not in the caffeine group. CL between caffeine and placebo groups was not significant at any tested time. 4. Amplitude of Pupil Constriction showed no changes.
Conclusion: Saccadic Velocity, Initial Pupil Diameter and Constriction Latency all showed significant changes. Of the oculometric measures assessed, Saccadic Velocity showed the largest number of significant changes with slowing beginning at 19.5 hours of continuous wakefulness. No significant differences for any measure were seen between placebo and caffeine groups. Changes associated with extended wake-

fulness were seen more frequently in the placebo group than in the caffeine group, with slower saccadic velocities in the placebo group at three post-caffeine time points, and a trend towards significance, suggesting that caffeine may be mitigating the effects of continuous wakefulness on some oculomotor measures.

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Visual Perception and Simulated Flight Performance Impairments in Pilots during Continuous wakefulness of 26 hours are Correlated

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Introduction: Visual perception, simple reaction time (psychomotor vigilance), and flight measures in an air-refueling simulator were evaluated over 26.5 hours of continuous wakefulness in US Air Force pilots in order to examine the effects of one overnight of wakefulness on the relationship between visual perception, psychomotor vigilance and complex motor performance. It was hypothesized that visual perceptual impairments would correlate with slowing reaction time and motor impairments during this period of sustained wakefulness. The intent was to provide information for physicians, aeromedical safety personnel, and researchers to model, monitor, or predict performance in fatiguing operational environments.

Methods: Eight military pilots (m, 31-52 y/o, mean 37yrs) on flight status were recruited to perform the primary task of flying a simulated 12.5-hours overnight mission after a day of continuous wakefulness and the secondary task of responding to repeated 20-minute presentations of single- and double-light stimuli displayed in random sequence in an arc 75-degrees-left to 75-degrees-right of center of the head. The task consisted of 150 light stimuli, each 0.25 second in duration presented while the pilot maintained an airspeed of approximately 275 knots 50 feet behind and below the tanker. Responses to the stimuli were verbal and manually recorded. On study Day 1 the volunteers re-familiarized themselves with the simulator functions, trained on the tasks, and were allowed 6 hours of time-in-bed overnight. On study Day 2 subjects remained active throughout the day and at 8 pm began a 12.5-hour simulated flight. Complex performance was measured through deviations from a pre-established azimuth heading during the visual perception task. Azimuth deviations were also measured during four 15-minute refueling periods. Simple reaction time was measured using the Psychomotor Vigilance Task (PVT) during crew rest periods. Correlation analyses are preliminary.

Results: Significant visual perceptual impairment and significant complex motor performance impairment, as measured by azimuth deviations, each began at 19 hours of continuous wakefulness. Significant simple reaction time (PVT) decrements began at 19.5 hours. Correlation between impairments of visual perception (total omissions) and impairments of complex motor performance (total # azimuth deviations) was significant at < p=0.0001, (r2=0.87). Correlation between total omissions on the visual perception task and reaction time was significant at < p=0.0003, (r2=0.66); and between reaction time and complex motor performance was p=0.0003, (r2=0.65). Impairment in air refueling (azimuth deviations during air refueling) achieved significance in the final refueling period.

Conclusion: Impairments on a visual perception task and on a complex motor performance task (during pre-contact periods) begin at 19 hours of continuous wakefulness. Impairments of refueling (contact periods) begin at 23 hours of continuous wakefulness. Visual perceptual and complex motor skills task impairments are more closely correlated than either is to slowing on a simple reaction time task. The implications are that data from higher order perceptual and complex motor tasks may provide more realistic inputs for models intending to monitor and predict performance declines in operational environments.

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On Interrelation Between the REM Sleep Need and Learning

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Introduction: Over half a century since REM sleep (REMS) discovery, many an original work has been devoted to studying this sleep stage relation to memory. However, it has not been established yet whether REMS is indispensable for learning and consolidation of memory traces. This work was aimed at clarifying interrelationship between need for REMS and learning. The investigation was conducted in two directions: 1, study of changes in the amount and quality of REMS in posttrial sleep-wakefulness cycle (SWC) and 2, study of variation of REMS propensity during its elimination following learning sessions.

Methods: Two groups of mature male cats (n=6 in each group) were chronically implanted with electrodes for EEG, EOG and EMG recordings. Animals, after post-surgery recovery and adaptation to experimental setup, were recorded in a digital multichannel polygraph system. After establishment of SWC baseline structure for each cat, learning sessions were run for the elaboration of conditioned instrumental alimentary reflexes in a specially designed experimental chamber consisting of the back-starting and front section equipped with feeders. Tone served as a directing conditioned signal (CS) to one feeder, click to the other. After delivery of CSs animal was required to make for feeders. In each session 10-fold reinforcement of a CS with a piece of meat was made at correct choice of the feeder corresponding to the CS. After 100 % CS discrimination had been achieved, learning was considered to be completed. Following each learning session one group of animals could fully realize SWC without any intervention, while the other group at the every REMS onset was awakened by electrical MRF stimulation during 6 hours. The various SWC phases were scored in wake, SWS and REMS. Their percent ratio, latency and frequency of REMS, number of PGO and REMs were determined. The data obtained were compared to relevant baseline data. Statistical significance was assessed using paired t-test.

Results: Analysis of posttrial SWC structure suggests lack of any consistent changes. In some cases there was a decrease in the time of first SWS onset leading to shortening of subsequent REMS latency; REMS mean duration and latency not differing from baseline values. No difference was found between baseline and posttrial SWC either in the percentage of various phases; the share of REMS in 6-hr periods not altering considerably, the orchestration of REMS with PGO and REMs did not enhance either. REMS-deprived animals exhibited no disposition to REMS, in particular number of forced awakenings from REMS following learning sessions did not substantially vary from REMS frequency occurring in deprivation period without preceding trials of reflex elabo-

ration.
Conclusion: Recent literature indicates that REMS serves no specific role in the processing or consolidation of memory. This view is supported by the presented data, which show that learning is not followed by REMS increase in quantity or quality, on the one hand, and the REMS need does not increase during acquisition of new skills, on the other.

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Age Related Differences in Sleep State Transitions and Transition Duration in Rats Before and After Sleep Deprivation

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Introduction: Significant sleep changes occur with aging in many mammalian species. One approach to defining the mechanisms for these changes includes examining underlying sleep architecture by analyzing sleep state transitions and durations.
Methods: Four young (3.5mo) and four old (21.5mo) Sprague-Dawley rats were maintained on a 12:12 light:dark cycle. The protocol consisted of a 48h baseline condition, 12h lights-on sleep deprivation (SD), and the following undisturbed 24h period. Transitions and durations were tabulated from sleep recordings scored in 12-sec epochs as Wake (W), non-REM sleep (NREM), or REM sleep (REM) (Shiromani et al, Am. J. Physiol. 2000). Only significant differences (t-test) are reported.
Results: Two transitions, W to REM and REM to NREM, occurred rarely, making W to NREM and REM to W transitions approximately 100%. During baseline, old animals had more NREM to REM transitions than young: 51 to 18 during dark, 56 to 39 during light. But for NREM to W transitions, old had fewer: 38 to 41 during dark, 33 to 37 during light. W to NREM transitions were higher in old during dark (82 vs. 75) but lower during light (95 vs. 106). REM to W transitions for dark averaged 49 (old) and 26 (young), and l60 (old) and 50 (young) during light. During baseline dark, 58% of NREM bouts in old transitioned to REM while only 34% transitioned in young. During light conditions, 62% of NREM bouts for old transitioned to REM compared to 50% for young. Transitions for old and young rats differed significantly after SD. The number of NREM to REM transitions averaged 85 (old) and 65 (young) during dark and 62 (old) and 59 (young) during light. W to NREM transitions averaged 82 (old) and 75 (young) during dark with 95 (old) and 106 (young) for light. NREM to REM transitions for young rats increased during dark from 34% to 69%, a level higher than old animals during baseline. Old rats sustained a decreased NREM to REM transition rate throughout the 24h period post-SD. The percent of NREM transitioning to REM during dark decreased from 58% to 25% after SD, while during light conditions, transitions receded from 61% to 38%. After SD, old were less likely to have NREM to REM transitions (25%) than young (68%) in dark and during light (38%) compared to 56% for young. Old had more NREM to W transitions than young: 42 vs. 30 for dark and 56 vs. 38 for light. There was one significant difference between old and young rats in bout duration. Old averaged ~3.1 minutes for NREM bouts transitioning to W in baseline dark compared to only ~2.5 minutes for young.
Conclusion: The greater fragmentation of sleep in old rats, both during baseline and after SD, implies that an aging mechanism may result from a shift in the likelihood of transitions, rather than an alteration in transition durations. Increased state transitions in old rats may reflect a diminished capability to maintain a sleep or wake state, potentially resulting from a loss of activity in sleep-wake neurons.

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Infant Rats Deprived of Sleep Exhibit Increased Sleep Pressure and Homeostasis

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Introduction: Sleep-wake cycles in infant rats are characterized by brief periods of muscle atonia followed by brief periods of elevated tone. Behaviorally, atonia periods are accompanied by myoclonic twitches whereas high-tone periods are accompanied by high-amplitude motor activity (e.g., kicking, stretching). Sleep in infants is also accompanied by hippocampal theta activity as well as increased sensory thresholds. Here we examine the effects of sleep deprivation in 5-day-old rats to determine whether pups at this age exhibit increases in sleep pressure during deprivation and whether they exhibit homeostasis during sleep recovery.
Methods: Twenty-four 5-day-old Sprague-Dawley rats were used. On the day of testing, a pup was anesthetized with isoflurane and EMG electrodes were implanted in the nuchal muscle. In addition, two subcutaneous shock electrodes were implanted on either side of the thorax. After recovery in an incubator maintained at thermoneutrality (35 deg C), the pup was transferred to a thermoneutral testing chamber where it was lightly restrained in a supine position. The test consisted of 3 30-minute periods. During the first period, EMG activity and behavior (using a microcamera placed above the chamber) were recorded to digital videotape. During the second period, data from 8 pups were recorded as 1-second shocks were delivered in increasing intensity (from 0.1-0.4 mA) whenever atonia was detected by the computer; intensity was increased in 0.1 mA increments when pups were no longer aroused by the shock. Finally, during the final 30-minute period, data were recorded while pups were not disturbed. Two control groups were used: Shock Control pups were recorded identically to the Deprived pups except that shock intensity was fixed at 0.1 mA; No-Shock Control pups never received shocks.λ°
Results: Pups in the Deprivation group exhibited lower rates of twitching than pups in either control group and exhibited increases in sleep pressure as deprivation continued. This increased pressure was evidenced by the need to increase shock intensity to prevent twitching and maintain high muscle tone. Pups in the Shock Control group experienced more shocks than pups in the Deprivation group but, because intensity was not increased, they were not deprived of sleep. During the recovery period, there were no discernible differences in the duration of atonia periods exhibited by pups in any group. Preliminary data suggest, however, a marked increase in the intensity of myoclonic twitching in the Deprivation group during the first 5 minutes of recovery.
Conclusion: Using a novel technique for depriving infant rats of active sleep, this is the first demonstration of increased sleep pressure in infants. By delivering shocks during periods of muscle atonia, pups were deprived of atonia and myoclonic twitching for 30 minutes. Using this procedure, marked increases in sleep pressure were found in the Deprived pups. Moreover, during recovery, there was evidence of rebound in the form of increased twitching. Together with previous findings, it is becoming clear that sleep in infant rats shares many of the basic characteristics of sleep as in adults, including increased pressure during deprivation and homeostasis.

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Effect of Prolonged Sleep Deprivation on Emotion Processing

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Introduction: While many studies have investigated total sleep deprivation (TSD) effects on mood changes and/or cognitive functioning, few have examined the effects of TSD on emotion processing. We investigated the effects prolonged TSD on the ability to identify emotions in faces.
Methods: To date, five healthy adults (mean age 24.6, range 21-32; 4 female) have completed this ongoing research. Participants lived in the sleep lab for 5 straight days, including 64 hours of continuous wakefulness. Participants completed a 2-part emotion-processing test at 9 hours (baseline), 22 hours, 40 hours, and 44 hours of TSD. During the test, participants are shown faces one at a time, each expressing one of 7 different emotions (Anger, Disgust, Fear, Happiness, Neutral, Sadness, and Surprise). In the first part of the test (explicit processing), subjects responded 'yes' or 'no' to whether each face expressed a target emotion. In the second part of the test (implicit processing), participants identify the gender of faces, irrespective of emotional expression. Response time (RT) and accuracy were recorded.
Results: Overall accuracy of identifying emotions decreased monotonically with increasing TSD (baseline: .90±.04, 22 hrs TSD: .88±.05, 40 hrs TSD: .87±.04, 44 hrs TSD: .77 ±.12) and RT increased with TSD (1009±58ms at baseline to 1132±123ms at 44 hrs). During explicit emotion processing, accuracy decreased the most, (BL - 44 hrs TSD) for identifying angry (.25±.31) and fearful (.18±.21) faces and the least for identifying happy (.05±.04) and neutral (.03±.07) faces. RT increased the greatest from BL to 44 hrs TSD for identifying angry (226±276ms) and sad (242±267ms) faces and the increased the least for identifying happy (25±229ms) and surprised (49±186ms) faces. Similarly, for implicit processing, RT to happy faces increased less than RT to the other emotions.
Conclusion: These preliminary results suggest that TSD interacts with the ability to identify facial expressions of emotion differently depending on the emotion displayed. Identification of happy faces appears least affected by sleep deprivation on both explicit and implicit levels. These preliminary findings are consistent with a multitude of research stating that happy faces are typically the most easily identified emotion, thus potentially making that ability the most resistant to effects of TSD. Differential effects of TSD on emotion recognition hold implications for police and military personnel working on little or no sleep. Increasing the sample size will help clarify these differential effects.

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Inter-Individual Differences in Impairment from Sleep Loss: Different Dimensions to Neurobehavioral Function

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Introduction: Previous studies in our laboratory have demonstrated traits for inter-individual variability in neurobehavioral changes during sleep deprivation. Impairment from sleep loss depended not only on the individual at hand, however, but also on specific neurobehavioral outcomes. We used a factor analysis approach to determine if different tests had common underlying neurobehavioral dimensions.
Methods: Performance deficits on neurobehavioral tasks were assessed for n=21 subjects (age 29.5±5.3; 9 females) during 36 hours of laboratory-based sleep deprivation, which each subject was exposed to three times at 2-week intervals. During the 7 days prior to each deprivation, subjects were required to spend 12 hours (22:00–10:00; sleep satiation condition) or 6 hours (04:00–10:00; sleep restriction condition) time in bed per day. Each subject had the sleep restriction condition once and the sleep satiation condition twice, in randomized balanced order. Subjects underwent neurobehavioral assessments every 2 hours during the 36-hour sleep deprivation periods. Data from the last 24 hours of sleep deprivation were averaged to determine changes in objective and subjective neurobehavioral outcomes across the circadian cycle. For this report, data were considered only for the two sleep satiation conditions. Since vulnerability to performance impairment from sleep loss was found to be trait-like, the results for these two exposures to sleep deprivation could be averaged without eliminating the inter-individual variability. Thus, a single value representing differential vulnerability to neurobehavioral impairment was obtained for every subject, for each neurobehavioral test. The assessment battery contained the following tests: serial addition/subtraction task; digit symbol substitution task; word detection task; repeated acquisition of response sequences task; psychomotor vigilance task; Karolinska Sleepiness Scale (administered twice); visual analog scales of fatigue and mood (administered twice); and performance and effort scales.
Results: A principal facor analysis with orthogonal varimax rotation was performed to determine to what extent between-subjects variability was consistent among different neurobehavioral tests. According to the scree plot of eigenvalues, three factors explained most of the variance. Eight neurobehavioral tests clustered on the first factor (loadings >0.72); these were the eight self-rating assessments. Four tests clustered on the second factor (loadings >0.65); these were the serial addition/subtraction task, digit symbol substitution task, word detection task, and repeated acquisition of response sequences task, which all appeared to depend on cognitive processing speed. The third factor captured the remaining test, the psychomotor vigilance task (loading 0.67), which was designed to measure behavioral alertness via sustained attention.
Conclusion: We had previously observed that inter-individual differences in vulnerability to deficits from sleep loss varied among neurobehavioral outcomes. These inter-individual differences were found to cluster on three distinct neurobehavioral factors: self-report, cognitive processing speed, and behavioral alertness. While self-report measures may be confounded by report bias, the emergence of the other two factors suggests the existence of two neurocognitive mechanisms underlying the performance deficits from sleep loss in the assessment battery that we used. This finding may have important implications for understanding the neurobiology of sleep and cognitive vulnerability to sleep deprivation.

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Effects of Chronic Sleep Restriction and Circadian Phase on Sleep Physiology

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Introduction: Changes in sleep physiology due to chronic sleep restriction and circadian disruption have been reported. The majority of these studies have been relatively short (<4 days), investigating either the effects of nocturnal sleep restriction or the effects of circadian disruption independent of sleep restriction. The aim of the present study was to investigate changes in sleep physiology during chronic sleep restriction with sleep periods placed at different circadian phases.
Methods: A total of N=27 subjects (age 30.5±7.3; 10 females) completed 1 of 3 sleep restriction protocols. In group A, following 3 baseline sleep periods (8h TIB), subjects were allowed 14 nights of 6h TIB from 01:30 to 07:30. In group B, subjects were allowed 2 baseline sleep periods (8h TIB), separated by 20h of TSD and followed by 10 nights of 6h TIB from 05:30 to 11:30. In group C, subjects were allowed 2 baseline sleep periods (8h TIB), separated by 28h of TSD and followed by 10 nights of 6h TIB from 13:30 to 19:30. Subjects remained in the laboratory throughout the protocol, with light levels <50lx (<1lx during scheduled sleep) and ambient temperature at 24±1°C. Polysomnographic recordings were made on all baseline days, and on 2 out of every 3 days throughout the restriction period. Records were scored using conventional criteria. Differences in sleep variables across days and among conditions were assessed using repeated-measures ANOVA.
Results: For total sleep time (TST), there was a main effect of day ($F[5, 100]=4.2$, $p<0.01$), and a day by condition interaction ($F[10, 100]=2.7$, $p<0.01$). Post-hoc analyses (independent samples t-tests for equality of means, equal variances not assumed) revealed that group C slept less than group A on restriction days 1 and 4 ($p<0.05$), and less than group B on restriction days 1 and 2 ($p<0.05$). Group A slept less than group B on the second night of restriction ($p=0.01$). There was a day by condition interaction for slow wave sleep (SWS) ($F[10, 110]=3.3$, $p<0.01$), with group B having less SWS than group C on restriction day 4 ($p<0.05$). There was a trend for a main effect of day for REM ($F[5, 105]=2.1$, $p=0.09$).
Conclusion: These results suggest that despite increased homeostatic pressure for sleep due to the acute period of TSD (28h) in condition C, subjects experienced a reduced TST during the first restriction day compared to the nocturnally placed (condition A) and delayed (condition B) sleep periods. The decreased SWS in condition C and increased REM in condition B relative to condition A may reflect circadian pressure for REM competing with homeostatic pressure for SWS. The results of this study must be interpreted in the context of potential changes of circadian phase over days of sleep restriction, which are reported elsewhere (Starzyk et al). These investigations are part of a larger study involving chronic restriction of sleep to 4h, 6h and 8h TIB at various circadian phases; analyses of these conditions are underway to further assess the effects of chronic sleep restriction and circadian phase on sleep physiology.

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Distinct Components of Sleep Structure at Baseline and Following 36 Hours of Sleep Deprivation

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Introduction: Previous studies revealed trait-like inter-individual variability in the structure of sleep. It has also been demonstrated that different aspects of sleep (e.g., REM, non-REM sleep) respond differentially to sleep deprivation. Here we distinguished independent components of sleep structure on the basis of trait inter-individual differences in sleep parameters at baseline and upon recovery after 36 hours of sleep deprivation.
Methods: As part of a larger study, n=21 subjects (age 29.5±5.3; 9 females) underwent two laboratory-based 36-hour total sleep deprivations at intervals of at least 2 weeks. Preceding each laboratory sleep deprivation, subjects were required to have 12h TIB (22:00-10:00) per day for 6 days. The night before sleep deprivation was spent in the laboratory, and also involved 12h TIB (22:00-10:00). After this baseline sleep period, subjects were kept awake for 36h, performing a 60min neurobehavioral test bout every 2h. Following deprivation, subjects were given recovery sleep with 12h TIB (22:00-10:00). The baseline and recovery sleep periods were recorded polysomnographically. Sleep records were scored fully blinded and according to conventional criteria. For every sleep record, we determined TST, S1-S4, REM, WASO, movement time (MT), sleep latency, REM latency (REML), and average sleep cycle duration (ASCD). We considered only sleep parameters that were stable between the two baseline records and the two recovery records, as evaluated by the intraclass correlation coefficient (ICC>0.5). WASO and sleep latency did not meet this criterion. The other sleep parameters were averaged over the two baseline records and separately over the two recovery records for each subject. Two subjects' data could not be used due to equipment problems.
Results: Principal factor analysis was performed to assess independent components of sleep structure in baseline sleep as well as recovery sleep. For baseline sleep, inspection of the scree plot of eigenvalues revealed that 4 factors explained the dominant part of the variance, with high factor loadings (absolute values >0.7) found as follows. First factor: REM (+0.93), TST (+0.74), REML (-0.76); second factor: S1 (+0.99); third factor: S2 (+0.96); and fourth factor: S4 (+0.96). For recovery sleep, 5 factors explained most of the variance, with high factor loadings found as follows. First factor: S2 (+0.94), S3 (-0.78); second factor: S1 (+0.90), MT (+0.75); third factor: REM (+0.87), TST (+0.86); fourth factor: ASCD (+0.85), REML (+0.78); and fifth factor: S4 (+0.94).
Conclusion: In the context of trait-like inter-individual variability, baseline and recovery sleep appeared to have four distinct components in common. These corresponded to REM sleep, slow wave sleep, stage 2 sleep, and sleep consolidation (with MT and S1 as inverse markers). In addition, recovery sleep showed a fifth dimension related to sleep cycle duration, which may reflect (inter-individual differences in) increased expression of both non-REM and REM sleep following sleep deprivation. These findings suggest that sleep structure is more complex than just sleep duration or a mere distinction between REM sleep and non-REM sleep, as is often assumed in conceptual and mathematical models of sleep architecture.

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Amphetamine Does Not Reverse Sleep Deprivation-induced Deficits in Defensive Responses

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Introduction: Studies on the neurobehavioral effects of sleep deprivation have demonstrated increases in sleepiness and deficits in various aspects of learning, memory and performance, but relatively little work has been done on the effects of sleep loss on more complex emotional and adaptive behaviors. The purpose of the present study was to confirm whether REM sleep deprivation (RSD) causes consistent changes in defensive responses and whether any sleep deprivation-induced abnormalities are reversed by amphetamine. We used the defensive burying test, which measures an innate response of rats to a noxious stimulus, involving both active and passive coping strategies.
Methods: Male Long Evans rats approximately 3 months of age were used. Animals were divided into home cage controls (H), apparatus controls (C), and REM sleep deprived (D), 6 to 8 animals per group. The flowerpot method was used to produce RSD. Each animal had multiple platforms to minimize restraint effects. The defensive burying test was administered on day 4 of RSD; the apparatus consisted of a testing cage lined with bedding, with an electrified shock probe inserted at one end. When the probe was touched, it delivered a shock (1mA). Animals were videotaped for 15 minutes after touching the probe. An observer blind to the identity of the rats recorded the time spent burying and in other behaviors (digging, grooming, rearing, prod exploration, chewing, freezing, rest, sleep and ambulation). For amphetamine studies, H and D rats received an i.p. injection of sterile saline or one of the following doses of (+)-amphetamine sulfate: 0.1, 0.5, or 2.5mg/kg dissolved in sterile saline 30 min before being placed in the testing cages.
Results: RSD significantly reduced burying behavior; the percentage of rats engaging in extended (>60 sec) burying was significantly lower in D rats than in H or C rats ($p<0.01$). D and C rats spent significantly more time grooming and digging ($p<0.001$) and had a shorter duration of freezing ($p<0.01$) compared to H rats; D rats showed a trend to spend more time grooming and freezing than C rats. Administration of amphetamine at the higher dose (2.5 mg/kg) in H rats decreased time spent burying, digging, and grooming. Amphetamine also increased ambulation and rearing. In D rats treated with amphetamine, burying behavior remained suppressed, but the RSD-induced increases in digging and grooming were reversed.
Conclusion: RSD resulted in abnormally short burying times. These results are consistent with effects of RSD on other behaviors in rats such as increased exploratory behavior and reduced shock-induced freezing that suggest abnormalities in defensive responses. Increased time spent grooming and digging were most likely indicative of increased sleepiness, as these behaviors generally precede sleep in rodents. Amphetamine reduced time spent burying in normal animals and did not reverse the sleep deprivation-induced deficits in this defensive response to an environmental threat. The amphetamine-induced reduction in grooming and digging, however, may relate to the known effects of amphetamine on reducing sleepiness. These data suggest that despite reducing sleepiness, amphetamines may have the potential to exacerbate other neurobehavioral deficits resulting from sleep deprivation.

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Effects of Sleep Deprivation on Attention: A Neuro-Imaging Study

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Introduction: The ability to shift attention is vital to spatial cognition, e.g. tasks of visual search, which are central to daily activities such as driving. Sleep deprivation has been shown to impair performance on a variety of attentional and spatial activities. To understand the effects of sleep deprivation on spatial attention, the current study used functional magnetic resonance imaging and behavioral measures while subjects performed a task requiring shifts of attention.
Methods: Six subjects (ages 18-30) were scanned in a 1.5 Tesla magnet while performing a Posner-type attentional task in both rested and sleep-deprived states. The order of scanning sessions was randomized and separated by a two week interval. During the task, subjects fixated centrally and responded to peripheral targets preceded by spatially predictive (valid), misleading (invalid), or uninformative (neutral) cues. Trials were organized as an event-related design. Both anatomical (T1) and functional scans (echo-planar images sensitive to BOLD contrast) were acquired. Functional data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience). Images underwent standard processing including realignment and normalization. Because subjects showed more head movement in the sleep deprived condition, trials that occurred during the 16 seconds preceding any movement over 1mm were eliminated from the analysis. Movement covariates were also included in the statistical design to model residual movement-related effects. Conjunction analysis revealed areas of common activation across all subjects. Activations to valid trials are reported, and contrasts were performed within each subject between the sleep-deprived (SD) and rested (R) states. Regions were considered significant at $p<0.05$ corrected across the brain volume.
Results: Subjects in a rested state responded significantly faster during the valid than in the neutral or invalid trials. This cue benefit disappeared following sleep deprivation (For "Cue", $p=0.032$; for "Sleep", $p=0.694$; for "Sleep×Cue", $p=0.063$; 2-way, repeated measures ANOVA). Furthermore, sleep-deprived subjects made significantly more false positive ($p=0.028$, paired t-test) and false negative ($p=0.007$) responses. During the sleep deprived condition, significantly higher bilateral thalamic activations were seen, which appeared to overlie the ventral lateral, pulvinar, ventral posterolateral, and dorsal medial nuclei and possibly the reticular nuclei. Some areas within the attention network including the right posterior cingulate gyrus, the right superior parietal lobule, and the right frontal eye fields showed increased activation during SD, while others such as the right parietotemporal junction and the right parieto-occipito-temporal junction showed decreased activation during the SD state.
Conclusion: The current study suggests that the neurobiological response to attentional shifts is altered by sleep deprivation. In particular, the thalamus is far more activated when subjects are SD. The thalamus is known to mediate sleep and arousal states via thalamo-cortical loops that alter cortical activity. Thalamic activity can also be affected via inputs from the brainstem arousal system and cortex. In this study increased thalamic activation may relate to the subjects' attempts to remain alert during task performance. Similar results have been seen during tasks of sustained attention and may reflect the role of the thalamus in both arousal and attentional systems of the brain.

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Bayesian Individualization of Biomathematical Predictions for Cognitive Performance Impairment from Sleep Loss

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Introduction: Considerable trait-like inter-individual differences in cognitive impairment from sleep loss have been documented. Current biomathematical models of sleep/wake and performance regulation do not take these differences into account. The existing population-average models might be tailored to individuals by modifying the model parameters, but this requires prior knowledge of the individuals' vulnerability to sleep loss. We investigated a different approach to individualization of biomathematical models, relying on the distribution of model parameters in the population at large (i.e., a population-distribution model) without requiring prior knowledge about the subjects at hand.

Methods: As part of a larger study, n=13 subjects (ages 27.7±5.4y) spent 20 days inside a laboratory. After two adaptation days and one baseline day with 8h TIB (23:30–07:30), subjects' sleep was restricted to 4h TIB (03:30–07:30) for 14 days. Performance on a psychomotor vigilance task (PVT) was tested every 2h during wakefulness. Daily averages (09:30–23:30) were computed for PVT performance lapses (RT=500ms). These data were described with a mixed-effects model: $y(t)=\alpha+\beta t\grave{e}+å$, where y stands for performance lapses, t denotes time (baseline day 0, restriction days 1–14), and å is normally distributed within-subject noise. Baseline and slope parameters α and β were assigned lognormal distributions, and non-linearity parameter è was assigned a normal distribution over subjects. The distribution parameters of these three model parameters were estimated by fitting the mixed-effects model to the data of ten of the available subjects (randomly selected). This established the population-distribution model underlying the present individualization approach. The remaining three subjects were set aside as "previously unstudied individuals." We employed Bayes posterior distribution estimation to predict the performance of these test subjects. This procedure considers the parameter distributions in the population-distribution model to make likelihood-based adjustments to the individual subjects' model parameters.

Results: Using the data acquired in the sleep restriction study, we simulated sampling the data for the three test individuals on a day-by-day basis. The model parameters were adjusted each day by means of the Bayes posterior distribution estimation procedure. One-day-ahead predictions were then made daily using the adjusted model parameters. These individualized one-day-ahead predictions were compared to the subjects' overall data sets, which showed the typical large inter-individual differences. We found that the predictions adapted readily to the profiles that later turned out to best characterize the individual test subjects across the 14 days of sleep restriction. Out of 42 one-day-ahead predictions (14 predictions for each test subject), the individualized predictions were more accurate 38 times (i.e., >90%) compared to predictions that would have been made by the corresponding population-average model. Assuming an a priori 50% chance of outperforming the population-average model, we thus achieved statistically significant improvement ($P<0.001$) of performance predictions with the Bayesian posterior distribution estimation approach.

Conclusion: Bayes posterior distribution estimation (or Bayesian forecasting) is a promising technique for tailoring biomathematical model predictions of performance impairment to individual subjects. This is important considering the existence of substantial trait-like inter-individual differences in vulnerability to sleep loss.

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Effects of 62-Hour Total Sleep Deprivation and Recovery Sleep on Cognitive Performance

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Introduction: As part of an ongoing study of the effects of 62-hours total sleep deprivation (TSD) on neurocognitive function, we assessed how cognitive performance changed as a consequence of sleep loss and recovery sleep. We expected cognitive performance to decline as a result of sustained sleep loss and that this decline would vary as a function of factors related to the type, time, and nature of test being presented.

Methods: Thus far, five healthy adults have participated (mean age=24.6, range 21-32; 4 female). The protocol consists of 6 inpatient nights and days: 2 nights sleep, 62 hours TSD, and 2 nights recovery sleep. Cognitive testing was conducted at regularly scheduled intervals throughout the day and night. In this report, data from a spatial working memory (SWM) and spatial attention task (SAT), a behavioral inhibition test (BIT), psychomotor vigilance task (PVT), an arithmetic working memory task (AWM), and a verbal learning task (VLT) were graphically analyzed using mean group performance data across testing intervals.

Results: Subjects performed the SAT, SWM, and BIT at 6 time intervals during the study. Subjects exhibited decreased reaction times on SAT and SWM following the first night of TSD. Decrements in accuracy on SWM started after 20 hours TSD, while similar decreases in accuracy were not seen on a qualitatively similar but easier SAT until after 56 hours TSD. Mean error rates on the BIT, an indication of disinhibition, increased after 20 hrs TSD and stayed elevated until after recovery night 2. The PVT, AWM, and VLT were performed at 10 time intervals. PVT results indicated no overall slowing of reaction times with TSD. Lapses on the PVT increased after 1 night TSD and again after 2 nights TSD. There was a mirror decrease in lapses after each recovery night. The AWM involved 3 types of serial subtraction: -1, -3, and -7. Accuracy for the -7s showed moderate declines, peaking at TSD day 2. On the VLT, free recall for words varied as a function of both circadian and homeostatic factors, with a general decrease in memory with increasing TSD, but better performance on PM vs. AM administrations during TSD. Most performance decrements fully reversed following one night of recovery sleep. However, attentional lapses and behavioral inhibition were more persistent and did not completely improve until after a second night of recovery sleep.

Conclusion: Given these descriptive data, it appears that 62-hour TSD does indeed have prominent and anticipated effects on cognitive performance. However, TSD and recovery sleep effects are moderated by task-related factors. For example, simple reaction times (PVT) did not slow with TSD, while choice reaction times (SAT, SWM) did. Also, accuracy on tasks emphasizing mostly attention (SAT, -1s) showed a decline only after 2 nights TSD or not at all. Tests with greater working memory demands (SWM, BIT) showed impaired performance with less sleep loss. Most tasks recovered after a single night of sleep, but poor inhibition persisted, suggesting the orbital frontal cortex may be particularly vulnerable to TSD.

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Deprivation Of Bilateral Sleep Induces EEG Asymmetry In The Fur Seal

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Introduction: Fur seals are semiaquatic mammals, which can sleep both on land and in water. While sleeping on land, fur seals show predominantly bilateral SWS as do all terrestrial mammals. While sleeping in water, they show mainly asymmetrical SWS similar to unihemispheric SWS in Cetaceans. The aim of this study was to determine whether it would be possible to increase the proportion of SWS with EEG asymmetry in seals sleeping on land by depriving them of bilateral high amplitude SWS.
Methods: Two northern fur seals (Callorhinus ursinus, one male and one female, weight 23 and 25 kg, both 2-3 years old) were implanted with EEG, EMG and EOG electrodes for polygraphic sleep studies. Seals were placed in a 1.5 x 1.5 m indoor enclosure where they slept on land. First, polygraphic recording was conducted during one baseline day. During next 3 days the seals were not allowed to sleep during the daytime. At night they were awakened each time when entered bilateral symmetrical SWS and were allowed to sleep when they showed slow wave EEG asymmetry. Then the seals were allowed to sleep one day as during baseline. We analyzed the data visually, scoring EEG in each hemisphere as desynchronization, intermediate and high amplitude synchronization for 20-sec epochs and computed the EEG spectral power for 5 and 20-sec epochs in the range of 1.2 -4.0 Hz.
Results: The deprivation procedure induced a significant decrease of bilateral high amplitude or delta SWS - from an average 31% in two baseline nights to 7% of night SWS in deprivation nights 1-3. The deprivation procedure caused the duration of SWS with interhemispheric EEG asymmetry increased from an average 5% of SWS during two baseline nights to 23 to 33% on the three deprivation nights. Under the deprivation conditions the percentage of SWS epochs with higher asymmetry index (power in left hemisphere - power in right hemisphere / power in left hemisphere + power in right hemisphere >0.5 or <-0.5) showed a 5-fold increase, confirming the results of visual scoring. The sleep deprivation procedure induced longer USWS episodes (3-10 min) in fur seals, which were not recorded under the baseline conditions. We have also found that EEG asymmetry in seals can be induced by presenting low intensity auditory stimuli, which do not induce full arousal. We did not observe any consistent changes in the daily amount of REM sleep in the seals under the baseline, deprivation and rebound conditions. The deprivation procedure did not result in any rebound of bilateral high amplitude SWS when uninterrupted sleep was again allowed.
Conclusion: In this study we have demonstrated that fur seals can be induced to exhibit a greater proportion of SWS with interhemispheric EEG asymmetry when they sleep on land by means of deprivation of bilateral sleep and applying appropriate sensory stimulation. Thus the fur seal is ideal animal for studying processes and neurophysiological mechanisms controlling and permitting switching between bihemispheric (terrestrial type) and unihemispheric (cetacean type) SWS.

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Heart Rate Activation During Spontaneous Arousals From Sleep: Effect Of Sleep Deprivation

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Introduction: Arousal (MA) from sleep is associated with an autonomic reflex activation raising blood pressure and heart rate (HR). Recent studies indicate that sleep deprivation may affect sympathetic tonus and vagal activity but little is known about such changes in autonomic response to MA. We examined the pattern of cardiac response to MA in sleep-deprived healthy subjects.
Methods: The total sleep deprivation protocol involved 64-h without sleep followed by two consecutive recovery nights, conducted with continuous behavioral and electrophysiological monitoring. Seven healthy male subjects participated in the experiment. MA were classified into four groups, i.e. MA>3<6 s, MA>6<10 s, MA>10<15 s, and MA>15 s, according to their duration. Pre-arousal HR values were measured during ten beats before MA onset, and the event-related HR fluctuations were calculated during twenty beats after MA onset. As index of cardiac activation, we measured the ratio of highest HR of the twenty beats after MA onset over the lowest recorded before MA (HR ratio).
Results: Sleep deprivation induces significant decrease in overall MA index in the first recovery night ($p=0.01$) with return to pre-recovery night level thereafter. Occurrence of MA induces typical HR oscillations in a bimodal pattern, tachycardia followed by bradycardia, for MA lasting less than 10 s. For MA lasting more than 10 s the pattern was unimodal with more marked and sustained HR rise. HR response was consistently similar across nights, during NREM and REM sleep, without difference between conditions. For MA lasting more than 15 s, a more sustained rise in HR was observed in the recovery nights, reaching, however, slight statistical significance.
Conclusion: Overall total sleep deprivation appeared to have no substantial effect on cardiac parasympathetic-sympathetic balance and on cardiac response to spontaneous arousal from sleep. Although preliminary, these results suggest that sleep deprivation may have little impact on cardiovascular risk in patients with sleep disorders.

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The Effect of Sleepiness on Error Processing: Lack of Awareness or Lack of Evaluation?

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Introduction: The behavioral, cognitive, and psychophysiological effects of extended wakefulness are well known. As time awake increases, errors become more common and are often attributed to lapses in attention. The error-related negativity (ERN) is a negative EEG deflection, occurring after errors. It appears to originate in the anterior cingulate cortex and is most easily observed in response-locked ERP averages. Scheffers reported reduced ERN amplitudes after 24 hours of wakefulness and attributed this to a failure to detect errors. However, Nieuwenhuis, using an anti-saccade task, has demonstrated that the ERN may occur even after subjectively unperceived errors. Also, compensatory slowing following errors, a classic behavioral outcome, was not

observed by Scheffers, while Nieuwenhuis reported post-error slowing only on perceived errors. Following the ERN, a positive deflection (error positivity, Pe) is also observed and is thought to reflect further evaluation of the error. Scheffers did not examine the Pe and Nieuwenhuis found a reduction only after unperceived errors. So, the question remains as to whether the reduction in the ERN after sleep deprivation was due to a lack of awareness (didn't notice) or lack of motivation (didn't care) and what effect sleepiness has on the Pe (error evaluation).
Methods: Two tasks known to elicit ERN's and Pe's (Flanker & Anti-Saccade) were administered to 17 women (aged 20-50 years) at two levels of alertness (3 & 22 hours awake). The Flanker task requires participants to quickly respond (ISI=1250 msec) via a forced choice key press to central target letters (H or S) from both congruent (HHHHH, SSSSS) and incongruent (HHSHH, SSHSS) arrays. The Anti-saccade task requires participants to focus on a central fixation point, then look away from a stimulus presented on either the left or right side of the computer screen. Amplitudes of the ERN and Pe where measured at the sites where maximal deflections typically occur (FCz and Pz respectively). Visual analogue scales (VAS) were used to assess subjective sleepiness, effort and performance after each task, and participants were asked to estimate the number of errors made in the Flanker task.
Results: After extended wakefulness, participants reported being subjectively sleepier ($p<.001$), and performing worse ($p<.01$), but showed no significant difference in effort ($p=.38$, $p=.46$) on both tasks, as shown by the visual analogue scales. Across conditions (3 vs 22 hours awake), they reported a similar number of subjective errors ($p=.80$) in the Flanker task which closely matched analysis of the objective errors ($p=.64$). For both tasks, the ERN (measured at FCz) was not significantly reduced by sleepiness (Flanker, $p=.50$; Anti-saccade. $p=.73$); however, the Pe (measured at Pz) was reduced after extended wakefulness (Flanker, $p<.001$; Anti-Saccade, $p=.02$). In the Flanker task, behavioral slowing after errors was larger in the alert than in the sleepy condition ($p<.05$). When error magnitude was considered in the anti-saccade task (median split based on EOG amplitude, small/large) the small errors produced significantly smaller ERN's regardless of level of alertness ($p=.02$).
Conclusion: These results show that after 22 hours of wakefulness, individuals react to both the existence, and the magnitude of their errors. This can be seen in the failure to find a significant reduction in the ERN across both tasks based on time awake, even though we did observe significantly smaller ERN's after small errors in the Anti-Saccade task. However, further evaluation of the error (reduced Pe), and remediation of these errors (behavioral data) may be impaired despite continued effort (VAS). In light of the fact that we failed to find any significant difference in effort or ERN amplitude across conditions, we conclude that although awareness (they notice), and motivation (they care), remain relatively intact; error evaluation (Pe) is impaired after extended wakefulness.

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Sleep Deprivation Affects Learning and Memory in Adult Zebrafish
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Introduction: Zebrafish is a genetically well-characterized diurnal vertebrate with a clear circadian pattern of daytime activity and nighttime rest (Cahill et al., 1998). Earlier, we have established that rest state in this animal can be considered a sleep-like state, based on important similarities with sleep in mammals, including characteristic postures, increased arousal threshold and rebound after sleep deprivation (Zhdanova et al., 2001). Given multiple transgenic and mutant phenotypes available and the current construction of genetic and physical maps of this lower vertebrate, zebrafish opens new possibilities in studying the physiological mechanisms and function of sleep behavior. Here we show that zebrafish can also serve as a model to investigate the effects of sleep and sleep deprivation on learning and memory.
Methods: Adult zebrafish (1 year old wild type Danio rerio; 12 fish/group) were tested. Locomotor activity patterns in individual home tanks and test chambers were documented using VideoTrack image analysis system (ViewPoint, France). Mild electric shock was used to reinforce conditioned place preference (CPP). Black color served as a conditioning stimulus. Non-stressful sleep deprivation was achieved by a constantly moving object in the tank.
Results: Nighttime sleep deprivation caused reduced daytime activity in home and test environment, affirming sleep rebound phenomenon in adult zebrafish. Daytime sleep deprivation did not produce significant alterations in overnight activity. Nighttime sleep deprivation altered CPP acquisition and extinction phase, resulting in increased number of entries and time spent in the zone associated with electric shock. No such effect of daytime sleep deprivation was documented.
Conclusion: Overnight sleep deprivation in adult zebrafish results in sleep rebound and adversely affects learning and memory in conditioned place preference test.

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Short Sleep Duration Is Associated With Reduced Leptin, Elevated Ghrelin, And Increased Body Mass Index (BMI)
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Introduction: Sleep is increasingly curtailed in modern society, but the health consequences of sleep loss are unknown. Sleep duration, however, is increasingly recognized as an important regulator of body weight and metabolism in animals and humans. A number of hormones regulate appetite, energy expenditure, and substrate metabolism. Two key opposing hormones in appetite regulation are leptin and ghrelin, which act at the same sites in the hypothalamus. Leptin is an adipocyte-derived hormone that depresses appetite, while ghrelin is predominantly a stomach-derived peptide that potently stimulates appetite. Other mediators of metabolism include adiponectin which is also secreted by adipocytes and is strongly associated with insulin resistance. The alterations in the above hormones that may mediate the interaction between sleep duration, appetite, and metabolism were investigated in a large population.
Methods: Protocols were approved by the institutional review board of the University of Wisconsin Medical School. All subjects underwent nocturnal polysomnography and reported on their sleep habits through sleep diaries and questionnaires. Morning fasted blood samples (n=1,024) were evaluated for serum leptin and insulin (by enzyme-linked immunoassay), serum total ghrelin and adiponectin (by radioimmunoassay), glucose, and lipid profile. Relationships between these measures, BMI, and sleep duration (habitual and polysomnographically defined) were evaluated using multivariate regression with control for confounding factors, including age, sex, and the apnea-hypopnea index (AHI).
Results: A quadratic relationship was observed between sleep duration and BMI. Sleep times below or above 7.9 hrs were associated with increased BMI (linear coefficient = -2.33, $p<0.01$; quadratic coefficient = 0.148, $p<0.02$). In a hypothetical 50-year-old male, typical of our population, an average sleep of 5 hrs vs. 8 hrs was associated with an

increase in estimated BMI from 30.0 to 31.2 (+4.1%). In the same hypothetical subject, reduced sleep was also associated with decreased leptin (-21.3% for habitual sleep 5 hrs vs. 8 hrs, $p<0.01$) and increased ghrelin (+14.9% for nocturnal [polysomnographic] sleep 5 hrs vs. 8 hrs, $p<0.05$) independently of BMI. No significant association between AHI and any of the measures studied (including measures of insulin resistance such as the Quantitative Insulin Sensitivity Check Index, QUICKI) was noted.
Conclusion: Despite the associated increased BMI, subjects with short sleep duration have reduced leptin and increased ghrelin. Based on our current understanding of the physiology of leptin and ghrelin, and previous studies on healthy volunteers, the observed changes in the levels of these hormones with sleep loss are likely to increase appetite. In modern societies, where chronic sleep restriction is common and food is widely available, changes in appetite regulatory hormones with sleep curtailment may therefore contribute to obesity. BMI and sleep duration may explain many of the previously observed relationships linking sleep-disordered breathing to alterations in metabolic hormones. Our results suggest that it may be possible to estimate sleep debt using peripheral hormone measurements. Altering sleep duration may be an important adjunct to preventing and treating obesity.

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Effort and the Prefrontal Cortex Following Self-Induced Sleep Loss in Female and Male Students

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Introduction: Performance deficits following sleep deprivation may result from reduced metabolic rates of the prefrontal cortex. Reductions in effort expended following sleep deprivation may be related to changes in activity of the prefrontal cortex. The purpose of this study was to determine whether there is a connection between naturally occurring sleep loss, functioning of the prefrontal cortex and effort.
Methods: Participants were 56 males and 73 females (mean age 21.8 years, range=18-51). Objective effort was measured using the Math Effort Task (MET) and a non-academic task choice question. A subjective effort question completed at the end of the battery asked, "Consider the maximum effort you had available to give to this task today. How much of that maximum effort do you think you gave to this task?" The Tower of Hanoi (TOH) task was used to assess functioning of the prefrontal cortex. The participants also completed a sleep diary, the Stanford Sleepiness Scale (SSS), the Profile of Mood States (POMS) and a simple reaction time task.
Results: Effort, as indicated by the difficulty level selected on the MET, was positively correlated with functioning of the prefrontal cortex as measured by the Tower of Hanoi task [$r(81)= .346$, $p=.002$]. Math difficulty level selected was negatively correlated with reaction time [$r(81) = -.422$, $p<.001$]. Effort, as measured by the difficulty level of the nonacademic task chosen, was negatively correlated with total mood disturbance [$r(129)=-.221$, $p=.017$]. Total mood disturbance was positively correlated with sleepiness [$r(129)=.573$, $p<.001$] and overall mood disturbance was greatest for the most sleep-deprived participants and least for those who slept more than 100% of their self-described optimal sleep [$F(2,127)=7.734$, $p=.001$]. When participants were divided into three groups; those who slept less than 76.9% of optimal sleep, those who slept between 76.9% and 100% of optimal sleep, and those who slept over 100% of optimal sleep, a sleep group x gender interaction on level of math difficulty selected was found [$F(4,125)= 4.959$, $p=.008$]. Females chose less difficult tasks when they obtained little sleep or more than their optimal amounts, while men chose more difficult tasks when they obtained little sleep or more than their optimal amounts. A sleep group x gender interaction [$F(4,125 = 4.171$, $p=.018$] showed that subjective effort reflected objective effort. Females reported expending more effort after sleeping 76.9% to 100% of optimal sleep while males reported expending more effort when they had below 76.9% or over 100% of optimal sleep.
Conclusion: Effort, as assessed by the choice of difficulty level on the MET, appears to be related to the functioning of the prefrontal cortex. Effort, as indicated by the choice of non-academic task to be performed, seems to be negatively affected by mood disturbance, which in turn is affected by sleepiness. Women and men differ in the effort they expend and the circumstances under which they expend it. Effort expended by the two genders is determined by the amount of sleep obtained relative to their reported optimal amounts. Further examination will attempt to articulate the relationship between sleep loss, sleepiness and mood changes, activity of the prefrontal cortex and effortful behavior.

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Is a Snorer Dangerous to the Bed Partner?

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Introduction: It is estimated that almost one third of adult population snore. Multiple studies documented the effect of snoring on a snorer. Snorers have increased incidence of hypertension, heart attack, stroke, diabetes mellitus, cardiac arrhythmia, as well as driving and industrial accidents. Bed partners of snorers suffer as well. Complaints of non-restorative sleep, signs of chronic sleep deprivation are common in people sharing living quarters with ones who snore. Snoring is not only harmful to the health of those who snore, but it is also negatively affect their social life. Sometimes it even destroys families.
Methods: During the period of January 23, 2002 - May 17, 2002 we studied the effect of treatment of patients with OSA and snoring on their bed partners. Eleven males and 7 female patients (ages 32-63 y.o.) with polysomnography - documented obstructive sleep apnea and snoring were interviewed twice: before initiation of CPAP therapy and 5 - 6 weeks into the therapy. Compliance with therapy (CPAP use for at least 4 times a week, 4+ hours a night) was documented by using the Encore Pro Smart Card (Respironics, Inc.). The bed partners of those patients: 11 females and 7 males (ages 26-61 y.o.) were also interviewed twice. The interviewer (Dr. Abderhalden-Friend) used the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) questions for all interviewees (36). The FOSQ questions covered five aspects of life: activity level, vigilance, sexual relationship, general productivity and social outcome.
Results: Improvement in snoring index, ESS score and all FOSQ parameters as a result of CPAP therapy were documented in all patients with OSA/snoring. Their bed partners also demonstrated significant improvement in ESS and all FOSQ scores. The Epworth Sleepiness Score improved: in patients - from 11.9 to 6.7, in bed partners - from 7.3 to 4.6. The total FOSQ score improved by 21.49% in patients and by 18.87% in bed partners. Improvement was documented in every parameter of the FOSQ for the patients / bed partners (%): activity - 28.24 / 23.28, vigilance - 28.41 / 25.76, intimacy and sexual relationship 19.15 / 33.13, general productivity - 15.98 / 16.19, social outcome - 17.62 / 2.37.
Conclusion: We conclude that OSA /snoring leads to excessive sleepiness in a bed partner and that treatment of OSA/snoring results in

improvement of excessive sleepiness and several social functions not only in the patient but in his/her bed partner as well.

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The Effects of 40 Hours of Total Sleep Deprivation on Inflammatory Markers

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Introduction: High circulating levels of pro-inflammatory cytokines and cellular adhesion molecules are reported to be independent risk factors for cardiovascular disease. In addition, sleep loss is reported to be associated with increased cardiovascular mortality and morbidity. While sleep deprivation produces a stress response, less is known about how sleep deprivation affects the immune system. Therefore, the purpose of this study was to examine inflammatory markers in healthy adults during 40 h of total sleep deprivation.
Methods: Twenty-one healthy men and women (29.1 ± 9.4 (SD) years) were scheduled to sleep for 8 h each night for three weeks at home and for three baseline days in the laboratory after which they were kept awake for a 40 h constant routine. Constant routine conditions included constant posture (25° head-up bed rest), dim light exposure (< 1.5 lux) and hourly nutrition intake. Blood was sampled via an indwelling intravenous catheter every 30 min. Plasma samples were stored at -80°C until assayed. Plasma samples were combined into hourly aliquots, and concentrations of pro-inflammatory markers: vascular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), E-Selectin, and C-reactive protein (CRP); the anti-inflammatory cytokine interleukin-1 receptor antagonist (IL-1ra); and the pro- and anti-inflammatory cytokine interleukin-6 (IL-6) were assessed using ELISAs from R&D Systems (Minneapolis, MN) and ALPCO (Windham, NH). Data were z-score transformed and trapezoidal area under the curve was calculated for hours 1-16 and hours 25-40 of wakefulness. These times of day correspond to times of habitual wakefulness and were selected to control for possible influences of circadian phase on inflammatory markers.
Results: Repeated measures ANOVAs showed that 40 h of total sleep deprivation significantly increased plasma concentrations of IL-1ra (mean z-scored area under the curve hours 1-16 = -3.34 ± 1.24, hours 25-40 = 2.28 ± 1.14; $p < 0.05$) and ICAM-1 (mean z-scored area under the curve hours 1-16 = -2.30 ± 1.01, hours 25-40 = 1.59 ± 0.77; $p < 0.05$); a trend for increased E-Selectin ($p = 0.067$); a trend for decreased CRP ($p = 0.067$); and non-significant decreased levels of IL-6 and VCAM-1 ($p > 0.10$).
Conclusion: The current results indicate that one night of acute total sleep deprivation alters circulating levels of pro- and anti- inflammatory immune cytokines and cell adhesion molecules. The consequences of the current findings for immune function and/or cardiovascular disease during sleep deprivation remain to be determined.

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Sleep Deprivation and Alcohol: A Model using Cognitive Tasks

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Introduction: Several studies have compared the effects of sleep deprivation and alcohol intake on performance. Several questions, however, remain regarding the validity of this comparison. Some researchers have pointed out that using data limited to fairly simple reaction time tasks, could impact the similarities observed between the effects of alcohol and sleep deprivation. It would be expected that some tasks may be more susceptible to sleep deprivation (e.g., vigilance tasks) than alcohol intake. As such, using different assessment tasks could have an impact on the similarities or lack thereof between sleep deprivation and alcohol intake. The purpose of this study was to use a model that predicts Blood Alcohol Concentration (BAC) based on performance on four different cognitive tasks under sleep deprivation conditions.
Methods: The participants were 23 college students who were paid to participate. The participants were sleep deprived for a total of 28 hours. During the last 18 hours of the sleep-deprivation period, the participants were brought into the laboratory and repeatedly completed a number of tasks. One of the tasks that they completed was the Automated Performance Test System (APTS). The APTS included 4 tasks that were used to predict BAC: math processing, grammatical reasoning, code substitution, and two-hand tapping. The APTS was completed at 4 separate times during the night. BAC was calculated by comparing the results in the latter 3 testing periods to the results from the first testing period. The first testing period took place between 5:30 and 9:30 PM on the night of sleep deprivation and was used as a control period. The remaining three testing periods (9:45 pm - 1:45 am, 2:30 - 6:30 am, and 6:45 - 10:45 am) occurred as the participants became more sleep deprived.
Results: BAC, as calculated from the APTS model, increased significantly ($p<.01$) over the last 18 hours of the sleep deprivation period. However, the calculated BAC levels were fairly small [9:45 - 1:45 AM was 0.009 (SD = .015); 2:30 - 6:30 AM was 0.016 (SD = .02); and 6:45 - 10:45 AM was 0.024 (SD = .022)]. Although the BAC levels were small, there was a trend for increasing BAC with increased number of hours of sleep deprivation.
Conclusion: The current study indicates that sleep deprivation results in performance that is similar to fairly low levels of BAC as based on the APTS model. Other studies comparing sleep deprivation to alcohol intake have reported higher levels of BAC. However, these studies used vigilance tasks which may have increased the effect of sleep deprivation in relation to the effect of alcohol intake. By using several well-known cognitive tasks, the current study permits a different approach to examining sleep deprivation effects in comparison to BAC.

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Caffeine Effects On Recovery Sleep Following Total Sleep Deprivation

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Introduction: Although caffeine is widely used to reverse alertness and performance decrements during sustained operations, caffeine's effects on subsequent recovery sleep are not well documented - effects that are potentially relevant because disrupted sleep may delay recovery from sleep deprivation-induced performance and alertness deficits. In this study, caffeine dose-response effects on daytime recovery sleep following 27h total sleep deprivation and subsequent psychomotor performance were evaluated. Because chronic caffeine use may alter caffeine's effects, habitual caffeine consumption also was considered.
Methods: Data were from 9 normal, healthy adults (6 habitual low [< 100 mg/day] and 3 habitual high [> 400 mg/day] caffeine users) who completed a randomized 4-session crossover design. After 20 hours of

wakefulness (0700 Day 1 to 0300 Day 2) subjects were administered caffeine 0, 100, 200, or 300 mg (Stay AlertTM gum chewed for 5 minutes). The same dose was repeated at 0500 and 0700 h. At 1000 h (27h sleep deprivation), subjects slept for 8h, followed by Psychomotor Vigilance Task (PVT) administration at 33 and 55 minutes post-awakening. Polysomnographic (PSG) data were analyzed for caffeine dose, habitual caffeine use (Low v. High), and recovery sleep segment (first, second, and third 160-minute segment); and PVT data (speed [1/RT]) and number of lapses [RTs > 500 ms] were analyzed for caffeine dose and habitual caffeine use using mixed-model analyses of variance (ANOVA) with Tukey HSD post hoc comparisons ($p<.05$). Due to lost PSG data, the 200mg condition was not included.

Results: Caffeine 300 mg decreased total sleep time (TST) compared to caffeine 100 mg ($p<.05$). Both caffeine 100 mg and caffeine 300 mg increased stage 1 minutes compared with placebo ($p<.05$; although HSD $p>.05$); and the 300 mg dose also increased stage 1 percent ($p<.05$). Caffeine 300 mg also delayed slow wave sleep (SWS) onset compared to caffeine 100 mg and placebo ($p<.05$). SWS minutes were reduced during the first third of the sleep period for caffeine 300 mg compared to placebo and caffeine 100 mg (Drug x Thirds, $p<.05$). Habitual Low caffeine users obtained less SWS (percentage of TST) compared to the High group, but only at the caffeine 300 mg dose (Drug x Caffeine Use simple effect, $p<.05$). For High caffeine users ST2 % was reduced at the 300mg compared to placebo and caffeine 100 mg (Drug x Caffeine Use simple effect, $p<.05$). Post-recovery PVT performance was unaffected by caffeine dose and habitual caffeine use.

Conclusion: Caffeine exerts mild deleterious effects on recovery sleep following total sleep deprivation. Further, caffeine's effects appear to be confined primarily to the early portions of the sleep period, possibly allowing for recovery from caffeine's effects later in the sleep period as suggested by lack of post-recovery-sleep performance deficits. However, in situations where recovery sleep is more severely restricted to fewer hours, caffeine's negative effects on recovery sleep might have a greater negative impact on post-recovery sleep performance. Previous suggestions that habitual caffeine use alters caffeine's effects were only partially substantiated, suggesting that such effects, if actually present, would be modest.

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Sleep Loss and Fatigue in Pediatric Residents: Self-Report of Sleep Patterns and Impact on Performance

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Introduction: The recently instituted ACGME work hour regulations represent an attempt to minimize the impact of occupational sleep loss and fatigue; however, little information exists regarding sleep patterns of residents outside of the work setting. In addition, few studies have examined in any detail the impact of variables such as gender and training level.

Methods: Pediatric residents from were tested during two separate sessions after a month of light/no call (LC) and post-call after a month of heavy (q 4 or q 5) call (HC). Before completing a battery of neurobehavioral tasks at each session, participants completed the Epworth Sleepiness Scale (ESS) and a survey regarding sleep and countermeasure attitudes and behaviors.

Results: A total of 34 PL-1, 2, and 3 level residents (mean age 28.7 SD 2.7, 18 women, 14 PL-1, 15 PL-2) completed the study. Mean ESS score was significantly higher in HC compared to the LC condition (10.9 SD 4.8 (range 2-21) vs 5.8 SD 3.8 (range 0-15), $p<.001$). In LC only, male residents reported higher ESS scores (7.7 vs 4.2, $p=.007$). ESS scores did not differ by training year (PL-1 vs PL-2,3). Almost half the residents in LC (47%) and 94% in HC reported sleeping < 8 hours at least 3-4 days per week during the past month; 40% (LC) and 97% (HC) reported sleeping < 4 hours at least 1 or 2 nights per week. During on-call nights, residents reported sleeping 3.3 hours (LC) and 2.2 hours (HC; ns). On the day post-call, LC and HC sleep durations were 9.0 hours and 9.7 hours (ns). Sleep durations for LC and HC non-call weekdays were 7.4 hours and 6.9 hours ($p<.001$); for non-call weekends they were 8.1 hours (LC) and 8.5 hours (HC) ($p=.006$). Females reported sleeping longer than males during LC weekdays (7.8 vs 7.0 hours), and during both LC (8.5 vs 7.7) and HC (8.9 vs 8.0) weekends. Sleep duration did not differ by training level. Female residents were more likely than males to report that sleep loss and fatigue had a major impact on their personal life ($p=.05$). Overall, 61.8% of the residents felt sleep loss had affected their medical decisions, 47.1% reported having written an incorrect order, and 38.3 % having made medical errors specifically due to sleep loss. In addition, 73.5% worried about having a car accident driving home post-call, with female residents being significantly more likely than males to have this concern ($p=.003$). In terms of countermeasures, residents were more likely to nap (38.2% vs 14.7%; $X2=4.3$, $p<.05$) during the HC month, but caffeine use was not significantly different during the LC and HC months. Only 29.4% of the residents felt they had effective countermeasure strategies.

Conclusion: There appear to be significant gender differences in residents' sleep patterns and attitudes regarding the impact of sleep loss and fatigue. Overall, residents appear to lack effective strategies, including adequate recovery sleep, to address these effects, suggesting the need for resident training programs focusing on sleep education and effective countermeasure strategies.

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Defining Sleep During Pregnancy

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Introduction: The state of pregnancy is accompanied by various physiological alterations, including changes in sleep patterns. The immunological consequences of sleep deprivation are a growing concern and have received supplementary research attention in the last decade. However, despite the accepted notion by the American Academy of Sleep Medicine that pregnant women experience "an insomnia like sleep condition", there is sparse information describing, not only what constitutes abnormal sleep during gestation, but the immunological consequences for pregnant women who experience "excessive" sleep disruption and how these may affect pregnancy outcome. The purpose of this study is to develop a clinically justifiable definition of what constitutes a normal and abnormal sleeper during pregnancy and to explore various immune parameters associated with both the sleep process and pregnancy.

Methods: A sample of 34 pregnant women at various stages of pregnancy was recruited though the University of Colorado. Subjects completed sleep questionnaires (ESS, PSQI, and Additional Sleep Questions) and provided a blood sample. In addition, each subject kept sleep diaries for 2 weeks following the blood collection. All data were collected at 12-16, 22-26, and/or 36-40 weeks of pregnancy. Determination of "normal" and "abnormal" sleepers was based on clinical definitions of sleep onset latency (SOL) and wake after sleep onset (WASO). Subjects who had a SOL > 15 minutes and/or a WASO > than 20 minutes were defined as "abnormal" sleepers. Subjects who had a SOL of < 15 AND a WASO of < 20 minutes were defined as "normal" sleepers. Serum levels of TNF- α, Il-4, IL-6 and IL-10 were determined

using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Biosource Europe).
Results: Frequencies revealed an equal number of normal (n = 7) and abnormal sleepers (n = 7) in the1st trimester; while for the 2nd and 3rd trimesters there were more abnormal sleepers (n = 15 and 11, respectively) than normal sleepers (n = 9 and 2, respectively). Due to the small sample size, data were collapsed across pregnancy for SOL, WASO and the four immune measures: IL-6, IL-4, IL-10 and TNF-a. Collapsing the data across pregnancy revealed a similar picture (21 abnormal sleepers and 10 normal sleepers). An initial analysis of the immunological data revealed few significant results. There was however, a significant increase, as expected, in serum TNF- α in abnormal sleepers (M = .279) compared to normal sleepers (M = .169) (t = 2.486, p = .02).
Conclusion: Sleep is undisputedly disrupted during pregnancy. Sleep deprivation is known to alter immune profiles in healthy subjects, but little data is available regarding sleep patterns and immunological consequences on maternal health or pregnancy outcomes. This pilot data revealed alterations and variations in sleep and immune parameters for pregnant women. TNF- α, a sleep associated cytokine, was elevated in abnormal sleepers during pregnancy. This ongoing study is beginning to address these issues, but additional data must be collected to examine the relationships between sleep disruption, immune function, and pregnancy outcome.

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Frontal Lobe Function Deficits After Sleep Deprivation, During Estimated Nadir And Apex Of The Circadian Clock

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Introduction: The effects of partial sleep deprivation on frontal lobe functions can be subtle and therefore difficult to detect. Furthermore, when taxed during the subjective night, frontal lobe function appears relatively preserved. Perhaps neither of these conditions alone is adequate to unmask frontal deficits. By asking subjects to perform both during the subjective night and under conditions of sleep deprivation, we hoped to uncover clearer signs of frontal lobe deficits in cognition.
Methods: Exclusion criteria: history of head injury; travel across 2 or more time zones within 6 weeks; history of psychiatric medication usage in prior 12 months; history of sleep disorder in S or 1st degree relative. Subjects (n=14, 18-24 yrs, 6 males) kept sleep diaries and wore actigraphs for 4 days prior to testing. ANOVAs and chi-square indicated no group differences on age (F=1.03, p< .87), prior sleep history (F=2.8, p<.12), or gender (?2 = .73, p< .70). Controls (n = 4) were tested before and after a normal night of sleep at 17:00 both sessions. The partial sleep deprivation group (PSD, n = 6, in bed 00:30 - 04:30) was tested at 04:45 and 16:45, as was the total sleep deprivation group (TSD, n = 4). Tests of frontal lobe function, focusing primarily on executive function and working memory, included the Wisconsin Card Sort Task (WCST), the Paced Auditory Serial Addition Test (PASAT), the FAS, and the Stroop Color-Word test.
Results: Mean errors on the WCST decreased from Trial 1 to Trial 2 across all groups (mean, sd) as follows: Controls: -12.5 (18.5); PSD: -4.8 (5.4); TSD: -0.5 (4.2). Effect sizes ranged from .58 - 1.1. On the PASAT, subjects demonstrated mean total correct responses (sd) between Trial 1 and 2 (across all speeds) by groups as follows: Controls: + 23.8 (11.8); PSD: +13.2 (9.8); TSD: +7.3 (20.3). Effect sizes ranged from 0.4-1.03. On the FAS, the TSD group had significantly more mean words total between trials (106, sd=19.5) than either the controls (79, sd=8.2) or the PSD group (81, sd=11.5) (F=5.17, p<.03). On the Stroop, the TSD group had improved naming time on both color swatch and ink color tasks as compared to the other groups.
Conclusion: Differences among groups consistently indicated that increased sleep deprivation, coupled with performance during the subjective night, lead to frontal lobe deficits in learning on 3 of the 4 dependent measures. Effect sizes were substantial. Frontal deficits may be more easily detected when conditions include both sleep deprivation and performance during the circadian trough.

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Age, Simple Reaction Time And Sleep Deprivation

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Introduction: Sleep deprivation is known to impair cognitive functions. Of the many tests of cognitive function, reaction time testing is a highly sensitive measure of sustained attention, which is a fundamental prerequisite for safe performing. Age is known to affect reaction time and older subjects perform significantly slower than young subjects in normal conditions, but this difference between performances does not seem so clear under sleep deprivation. Because young subjects are frequently involved in sleep related accidents one could speculate that young drivers are more affected than older drivers by sleep loss and therefore worsen their driving skills quicker. Another possible explanation for this age effect could be a difference in the perception of their level of impairment in dangerous conditions.
Methods: 10 healthy young male subjects (mean age 22.5 years) and 10 healthy older male subjects (mean age 58.2 years) were tested in two different conditions : after controlled usual sleep (rested), and after a full night of sleep deprivation. In rested condition, subjects were in bed from 23:00 to 07:30 H. In the sleep-deprived condition, subjects were monitored in the laboratory from 21:00 to 08:30 H. Subjects were tested every 2 hours (9H, 11H, 13H, 15H, 17H, 19H). They performed a 10-minute simple reaction time test on a PALM personal organizer. 130 black squares were displayed on the screen at randomized (2-7 s) intervals, over 10 minutes. The subject s task was to respond to the stimuli by pressing a key to turn the square off.
Results: Older subjects increased by 3.9 times (95%CI 1.5 _ 9.8) the risk of lapses compared to young subjects ($p < 0.004$). Sleep deprivation also increased by 1.9 times (95%CI 1.3 _ 2.7) the risk of lapses ($p < 0.001$). Young subjects: A negative binomial regression using number of lapses per session per subject as dependent variable and sessions and sleep condition (rested versus sleep deprived) as determinants, clustered on subjects showed a significant effect for sleep condition. Sleep deprivation increased by 1.9 times (95%CI 1.3 _ 2.7) the risk of lapses ($p < 0.001$). Older subjects: A negative binomial regression using number of lapses per session per subject as dependent variable and sessions and sleep condition (rested versus sleep deprived) as determinants, clustered on subjects showed a significant time effect. Lapses increased by 1.14 times (95%CI 1.0 _ 1.3) per session over the 6 sessions ($p < 0.008$).
Conclusion: The novel and interesting part of our study relies on the differences observed between young and older subjects under sleep deprivation. If young subject s reaction times are significantly better than the ones of older subjects when rested, sleep deprivation affects significantly the young whereas older subjects do not significantly alter their performances. Because reaction time is an important component of adaptative response in real world activities one could speculate from our results that sleep related accidents do not simply affect young drivers because of a higher exposure of this age group to sleep restriction, but also because of a higher sensitivity to sleep loss.

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Effect of Extended Wakefulness and Recovery Sleep on Thyroid Axis Activity

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Introduction: Thyrotropin stimulating hormone (TSH) secretion reaches a nocturnal peak shortly after the onset of sleep, and sleep loss is reported to have an attenuating effect on TSH levels. T3 levels have been reported to increase rapidly during sleep deprivation, and remained elevated, while T4 levels have been found to increase more gradually. We sought to investigate the effects of 3 nights of total sleep loss and partial sleep loss on thyroid hormones, as well as the nature of nocturnal and diurnal thyroid responses to recovery sleep following deprivation.
Methods: Twenty-two healthy, male adults (m=28.5y, range=21-47y) completed a 10-day laboratory protocol. Following 3 nights of baseline sleep, subjects were randomized to either 88h total sleep deprivation (TSD) or two 2h naps (NAP) per day (02:45-04:45 and 14:45-16:45) for 88h, followed by 3 recovery nights for sleep. Blood samples were collected at 90 minute intervals via an indwelling venous canula from the final baseline night, through the 88h sleep deprivation period, and to the end of the first recovery day. Plasma levels of TSH, T4, and T3 (via RIA) were then determined at 3h intervals. Differences in the plasma thyroid hormone levels during nocturnal periods and diurnal periods across the 5 days of the protocol (baseline 3 through recovery 1) were compared using paired t-tests and ANOVA.
Results: There were few differences in levels of TSH, T3 and T4 between the NAP and TSD conditions, hence analyses are reported for pooled data. As expected, sleep loss elevated plasma levels of TSH, T3 and T4 (all $p<0.05$). The first night of sleep loss resulted in elevated plasma levels of TSH (all $p<0.001$), but as has been reported elsewhere, these levels were reduced on the second and third nights of sleep loss relative to the first night of sleep loss ($p=0.029$ and $p=0.005$, respectively), with no difference between the TSH levels on latter nights (both of which remained above baseline; $p<0.057$). In contrast, T3 and T4 remained elevated across all nights of sleep loss. TSH and T3 levels (but not T4 levels) during the first recovery night of sleep were significantly below all 3 deprivation nights ($p<0.018$), but only TSH was below the baseline night during recovery sleep ($p=0.041$). Diurnal levels of TSH, T3 and T4 were slightly but significantly increased on the diurnal portion of deprivation days relative to the baseline day (all $p<0.05$).
Conclusion: The thyroid axis responded in a similar manner to 88h of total sleep loss and 88h of partial sleep loss in which 2h nap opportunities were possible every 12h, suggesting that the well known inhibitory effects of sleep on thyroid hormone measures require more than 2h of sleep to be evident. Consistent with previous studies, sleep loss resulted in elevated TSH, T3 and T4, but this effect was attenuated on subsequent sleep loss nights for TSH (but not T3 and T4). TSH was also markedly suppressed below baseline sleep levels during recovery sleep following sleep deprivation, consistent with recovery sleep being more hypometabolic than daily nocturnal sleep.

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A Theoretical Review On Proposed Functions Of Sleep

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Introduction: Since the inception of history, answers have been sought to one of the most basic of questions: Why sleep? A question that is both obvious and fundamental, and yet, a viable hypothesis has eluded humankind for millennia. This question has been approached at varying levels of analysis. Some have sought proximate answers; solutions that emphasize the mechanisms which regulate and enforce sleep patterning. Such endeavours are usually measured in the currency of physiology, biochemistry, or genetics. Conversely, others have addressed this question from an evolutionary perspective, the so-called ultimate questions. These questions attempt to answer the adaptive significance of sleep in terms of maximizing lifetime reproductive success. For a theory on sleep utility to be plausible, it must explain: 1. the specific sub-structures of sleep (eg. SWS, REM) across taxa and 2. the wide range of variation in sleep requirements both across and within taxa.
Methods: We conducted a review of sleep literature dealing with proposed functions of sleep. We summarized these data emphasizing commonalities of prevailing proximate and ultimate explanations of sleep utility.
Results: The literature review revealed diverse theories for both the functions of sleep and the architecture of the sleep cycle at micro (eg. molecular, cellular) and macroscopic (eg. neural systems, organismal) levels. Restorative theories (Hartmann, The Functions of Sleep 1973) presume that sleep functions to replenish concentration of a chemical (eg. a neurotransmitter, hormone) which is depleted during wakefulness. Protective theories suggest that specific neurons are taken offline during sleep, preventing neuronal exhaustion or that certain synapses require an idling period to regain sensitivity (Moruzzi, Brain and Conscious Experience 1966). Sleep may purge the brain of free radicals, detrimental to protein structure (Reimund, Medical Hypotheses 43:231-233 1994). REM may facilitate the development and maintenance of the oculomotor system important in coordinated eye movement (Berger, Psychology Review 76:144-64 1969) or reinforce neuronal connections responsible for instinctive behavior (Jouvet, Journal of Sleep Research 7:1-5 1998). Memory consolidation hypotheses propose that during sleep, shortterm memories are consolidated into longterm memories and that memories already in longterm storage are reinforced (Kavanau, Behavioural Brain Research 63:111-26 1994). Energy conservationists suggest that sleep limits a species' energy expenditure below that of its basal metabolic rate. Alternatively, immobilization theory (Meddis, The Sleep Instinct 1975) views sleep as a passive behavioral state that serves to keep an organism out of trouble and occurs when it has spare time. Specifically it suggests that sleep is an instinct, driving an organism to seek out its secure sleep site during periods when environmental conditions are incompatible with its existence. A recent study by Rattenborg etal. (Brain, Behavior and Evolution 58:323-332 2001) reveals that sleep and vigilance need not be mutually exclusive. Unihemispheric SWS is an adaptation in birds to permit environmental monitoring concurrent with the benefits of sleep.
Conclusion: Despite a plethora of hypotheses, no single theory can account for the myriad of relationships of sleep with constitutional and ecological correlates. Nor can any one theory explain the purpose for alternating SWS and REM sleep in animals, particularly mammals and birds where there is a large body of comparative data. It is now widely accepted, however, that sleep is more important, in a developmental and restorative context, to the brain than to the body. This may be an important clue in the search for an ultimate function for sleep. Conversely, a proximate sleep function is likely focussed at the level of the neuron or synapse rather than to the organ or tissue (Rechtshaffen, Perspectives in

Biology and Medicine 41:359-390 1998).

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Correlations Between Sleep Physiology and Neurobehavioral Performance Following Recovery from 88h Total Sleep Deprivation

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Introduction: Previous work has indicated that subjects who received 1 night of 14h TIB for recovery sleep had a greater improvement in neurobehavioral performance and subjective alertness than subjects who received 1 night of 7h TIB, following 88h total sleep-deprivation (TSD). In addition, providing 14h TIB relative to 7h TIB for recovery resulted in reduced homeostatic drive for sleep on subsequent recovery nights. This study examined the relationship between recovery sleep physiology and neurobehavioral performance after one night of recovery sleep (7h vs. 14h TIB) following 88h TSD.
Methods: Twenty-five adult males (mean 28.2y) lived in the laboratory for 10-days. Following 3 baseline days and nights (8h TIB), subjects remained awake for 88h, followed by 3 recovery days and nights. During the 88h TSD period n=13 were randomized to a caffeine intervention, and n=12 to placebo. Subjects were further randomized to two 7h TIB recovery nights followed by one night of 14h TIB (n=14) or three 14h TIB recovery nights (n=11). Lights-out for all sleep periods was 2330h. Subjects were tested on a 30min computerized neurobehavioral assessment battery every 2h of wakefulness throughout the study. Psychomotor vigilance task (PVT) number of lapses and Karolinska Sleepiness Scale (KSS) ratings after the first night of recovery sleep were evaluated for two periods of the day: 1000-1600h and 1600-2200h. Data were analyzed using a Pearson correlation coefficient.
Results: On recovery night 1, subjects in the 7h TIB condition averaged 6.68h TST, while those in the 14h TIB condition averaged 12.48h TST ($p<0.0001$). Paired t-tests revealed that subjects receiving one night of 7h TIB recovery reported feeling significantly sleepier and had significantly more lapses on recovery day 1 compared to baseline and recovery day 3 ($p<0.001$), whereas there was no difference between baseline and recovery days 1 and 3 for subjects receiving one night of 14h TIB. Across both 7h and 14h recovery conditions, there was only one reliably significant correlation: PVT lapses after recovery night 1 were inversely correlated with the amount of SWS ($r=-0.605$, $p<0.002$). When analyses were performed separately within each recovery condition (7h and 14h), PVT lapses were inversely correlated with SWS ($r=-0.600$, $p<0.05$), and KSS ratings were positively correlated with stage 2 sleep ($r=0.691$, $p<0.01$) for subjects receiving 7h TIB recovery, but not for subjects receiving 14h TIB recovery. Results did not change when partial correlations were performed to remove the influence of age on SWS.
Conclusion: Following 88h TSD, PVT lapses after the first recovery night of sleep were predicted by the amount of SWS obtained during the recovery sleep period, particularly when the recovery sleep period was limited to 7h TIB which was inadequate for full recovery. KSS ratings were predicted by the amount of stage 2 sleep obtained, but again only when sleep was restricted to 7h TIB. When TIB was 14h, which was adequate for recovery, no one aspect of sleep physiology was correlated with PVT or KSS markers of recovery. Further analyses are underway to examine other measures of performance and the effects of additional recovery sleep periods.

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Prediction Of Resilience To A Night Of Sleep Deprivation: Selected Traits And States

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Introduction: A night of sleep deprivation consistently and reliably diminishes mood and performance. Some individuals consistently are resilient to mood and performance decrements that result from sleep deprivation while others are severely impaired. These individuals have been referred to as type 1 and type 3 responders, respectively. Identifying responder types is salient to many institutions that rely on the success of sustained and long-term operations (e.g., DoD, NHTSA, FAA). Currently, the only means of identifying these types of responders is to assess outcomes following actual sleep deprivation. There is no known trait or personality type that consistently predicts decrements following sleep deprivation. Some studies have reported that Locus of Control (LoC) and several other trait variables may predict degree of decrement following sleep derivation, but these studies have not been replicated.
Methods: The relationship of a number of trait variables, including LoC, with self-report state variables both at rest and during exercise following a night of sleep deprivation or regular sleep among 13 males (19-27 yr) were examined. Testing sessions began in the morning within one hour of the participant's normal waking time. Sessions were randomized and crossed according to sleep manipulation and exercise or rest condition (2 x 2) and were separated by a week to allow for recovery. A week prior the sessions, participants completed trait questionnaires and were assessed for maximal oxygen consumption (VO2max) and ventilatory threshold (VT) via a ramped protocol on a cycle ergometer, to assess fitness and standardize the exercise workload (5% < VT).
Results: LoC did not predict degree of mood change (Bi-Polar POMS and its subscales, STAI-Y1, VAS for sleepiness ratings, and perceived exertion) associated with sleep deprivation as assessed from 2 (sleep manipulation) x 2 (dichotomized LoC) mixed model ANOVA (all ps > .21). This was the case for assessment just prior to condition or during condition. This lack of prediction held for other trait variables such as trait anxiety (STAI-Y2), behavioral inhibition and approach (BIS-BAS), negative and positive affect (PANAS), and fitness (VO2max, VT). Morning types (Morningness-Eveningness Scale) were more likely to experience a mood decrement after sleep deprivation compared to Evening types (Bi-Polar POMS Energetic, $p = .03$; Clearheaded, $p = .06$). This effect was most likely caused by the enhanced mood that Morning types reported after a normal night of sleep compared to Evening types. After a night of sleep deprivation mean self-ratings between types were equally low.
Conclusion: The selected trait variables do not predict affective resilience to a night of sleep deprivation among healthy college-aged males. Future studies should examine a broader range of traits and those with more extreme traits. Cognitive performance and psychophysiological methods should also be assessed and employed. Moreover, some personalities may benefit more from an exercise bout after sleep deprivation. These data are being analyzed and will be reported.

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Reductions in Circulating Growth Hormone and Prolactin Point to Altered Central Mechanisms in Sleep-Deprived Rats

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Introduction: Sleep loss in humans is associated with health impairments and shortened longevity by unknown mechanisms. Prolonged sleep deprivation in laboratory rats produces poor health indicated by (a) a negative energy balance, (b) central hypothyroidism, and (c) decreased resistance to infectious disease. Meaningful histopathological changes have not been found, hinting that multi-tropic factors may explain the apparent absence of localized pathology. Except for short-term studies, and beyond the thyroid axis, the effects of sleep deprivation on neuroendocrine systems are unknown. The present investigation characterized changes in major bursts of growth hormone (GH) and determined concentrations of insulin-like growth factor-1 (IGF-1), a GH effector molecule. Also determined were concentrations of prolactin (PRL), a cytokine that shares homology with GH, and corticosterone, a marker of hypothalamic-pituitary-adrenal (HPA) activation.
Methods: Adult male Sprague-Dawley rats were surgically prepared for polysomnography and for blood sampling through chronic indwelling catheters. After recovery from surgery and baseline measurements, rats were sleep deprived for 15 to 16 days by the Bergmann-Rechtschaffen method. The method entails motor locomotion of short duration (6 sec) upon sleep onset and noninterference with nonsleep behaviors to produce near total sleep deprivation. Simultaneous application of the same locomotive requirement to a second rat (yoked) produced sleep reduction. Major pulse characteristics and basal secretion of GH were determined by intensive blood sampling protocols in 4 experimental pairs. Integrative measurements of PRL secretion and pituitary stimulation of PRL release by exogenous thyrotropin-releasing hormone (TRH) also were employed. Plasma IGF-1 and corticosterone were determined in 8 experimental pairs. Baseline and experimental values were compared and are expressed as the mean ± standard deviation.
Results: High-amplitude pulses (>300 ng/ml), which composed 60% of GH pulses during baseline, were abolished by total, but not partial, sleep deprivation. Concomitantly, the average GH concentration decreased from 90 ± 28 ng/ml during baseline to 23 ± 6 (Week 1) and 20 ± 8 ng/ml (Week 2) in sleep deprived rats, compared to 62 ± 5 and 68 ± 13 ng/ml in yoked rats, respectively. IGF-1 showed a sustained reduction from baseline by >30% in sleep deprived rats, observed within the first 4 experimental days, while values were variable in yoked rats and ranged from +2 to -14%. Basal PRL was suppressed by -52 ± 39% and -45 ± 28 % during Week 1 and Week 2 in the sleep-deprived group, but tended to be above baseline in yoked rats. The magnitude of TRH-induced rise in PRL was unchanged. Corticosterone concentrations were unchanged.
Conclusion: Abolishment of high-amplitude GH pulses and suppression of GH, IGF-1, and PRL concentrations by sustained sleep loss likely contributes to health impairments, as in other clinical and experimental models of disease. Low IGF-1 concentration without a reciprocal increase in GH points to failed negative feedback at the level of the hypothalamus. Low basal PRL and a relatively normal proportional increase after stimulation suggest inhibition by the hypothalamus, rather than impaired pituitary storage. Unchanged corticosterone concentrations are consistent with previous reports and indicate the HPA axis is not likely mediating these neuroendocrine changes.

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Subjective Assessments during Chronic Sleep Restriction with Circadian Phase Adjustment

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Introduction: Several studies have described accumulating neurocognitive deficits during chronic sleep restriction. Subjective alertness and fatigue do not appear to display this continuing decline, but tend to reach levels of apparent 'adaptation'. The present study examined subjective assessments of alertness and fatigue during chronic sleep restriction with sleep at a delayed circadian phase.
Methods: Twenty-nine healthy subjects (16m; 13f; aged 21-45y) completed a 15-day study protocol. Following one baseline sleep (2330h-0730h) subjects remained awake for 20h, which was followed by an 8h delayed sleep (0330h-1130h). Subjects were then randomly assigned to a delayed sleep restriction condition (4h: 0730h-1130h, N=20; 8h: 0330h-1130h, N=9) for 10 consecutive days, which was followed by 2 nocturnal recovery sleep periods (2330h-0930h). Subjects remained in the laboratory throughout, with light levels <50lx (<1lx during sleep) and ambient temperature at 24±1°C. Every 2h during scheduled wakefulness subjects completed a neurobehavioural assessment battery, containing a range of subjective measures of sleepiness and mood: Karolinska Sleepiness Scale (KSS); Stanford Sleepiness Scale (SSS); visual analogue scales (VAS) to assess physical exhaustion, mental exhaustion and tiredness; and Profile of Mood States (POMS). Daily averages of alertness and mood were compared using repeated-measures ANOVA and post-hoc t-tests.
Results: All measures of subjective alertness and fatigue demonstrated a significant main effect of day ($P<0.003$) across the experimental protocol. Post-hoc analyses revealed significantly lower alertness and higher fatigue levels following the first restricted sleep period compared to baseline ($P<0.01$). For the KSS and the SSS there was a trend for a difference in sleepiness levels between the two restriction conditions ($F=3.49$, $P=0.073$; $F=3.29$, $P=0.081$, respectively), with increased sleepiness reported by the 4h group compared to the 8h group. In addition, a significant day by condition interaction was found for POMS fatigue ($F=2.74$, $P=0.032$), VAS physical exhaustion ($F=3.83$, $P=0.004$) and VAS tiredness ($F=3.55$, $P=0.004$). When considering the sleep restriction days only, with baseline not included, no significant effect of day was evident for any of the subjective measures. There was a significant effect of condition for the KSS ($F=3.94$, $P=0.057$), and a trend for condition differences for the SSS ($F=3.77$, $P=0.063$), POMS fatigue ($F=3.21$, $P=0.084$), VAS tiredness ($F=3.18$, $P=0.086$) and VAS physical exhaustion ($F=2.90$, $P=0.100$).
Conclusion: These findings may provide some insight into the nature of subjective assessments during chronic sleep restriction with circadian displacement. Early assessments of sleepiness and fatigue, in the period following an acute extension of wakefulness (20h compared to a normal day of 16h) and the initial move to the new sleep-wake schedule, were elevated compared to baseline. However, during the chronic phase of the study, when sleep-wake duration and sleep timing were constant, subjects did not report experiencing accumulating elevations in fatigue or sleepiness levels, within each sleep dose. We hypothesize that subjects may have used the self-report scales in a relative fashion, comparing their current situation to previous experiences.

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Predictor Variables of Vulnerability to Sleep Loss

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Introduction: This project aimed to identify psychological and sleep physiological predictors for the recently demonstrated trait-like inter-individual differences in vulnerability to neurobehavioral deficits from sleep loss.

Methods: 21 healthy subjects (age 29.5±5.3; 12 males, 9 females) participated in a study designed to investigate trait differences in vulnerability to sleep loss. As part of a larger design, each subject underwent 36h of laboratory-based sleep deprivation on two occasions separated by at least 2 weeks. Subjects were required to maintain a regular schedule of 12h time in bed (22:00-10:00) in the 7 days before each sleep deprivation, so as to satiate prior sleep need. Every 2h during the 36h sleep deprivation periods, subjects completed a 1h neurobehavioral test bout consisting of the Karolinska Sleepiness Scale (administered twice), visual analog scales of fatigue and mood (administered twice), serial addition/subtraction task, digit symbol substitution task, word detection task, repeated acquisition of response sequences task, psychomotor vigilance task, and performance and effort scales. Neurobehavioral outcomes were averaged across the last 24h of sleep deprivation and over the two sleep deprivation sessions, so as to yield a single measure of impairment per subject for each outcome variable. During sleep deprivation, core body temperature was recorded at 6min intervals by means of a rectal probe. The circadian phase and amplitude of the temperature rhythm, as potential predictors of vulnerability to sleep loss, were determined by fitting a two-harmonic sinusoidal curve. Prior to the experiment, subjects completed questionnaires measuring psychological and sleep physiological characteristics: Composite Scale of Morningness/Eveningness, Conflict-Stress Questionnaire, Epworth Sleepiness Scale, Eysenck Personality Inventory, Marlowe-Crowne Social Desirability Scale, Minnesota Multiphasic Personality Inventory-2, Multivariate Apnea Prediction Index, Myers-Briggs Personality Scale, Penn State Worry Questionnaire, Pittsburgh Sleep Quality Index, Sleep Disorders Questionnaire, Spielberg State-Trait Anxiety Inventory, and Survey of Work Styles. Scores on all subscales of these questionnaires were evaluated as candidate predictors of vulnerability to sleep loss.

Results: All candidate predictor variables were entered into a forward stepwise regression analysis of the individual neurobehavioral deficits associated with sleep loss. Introversion/extraversion as measured on the Myers-Briggs Personality Scale was a significant predictor of lapses (RT ≥ 500ms) on the psychomotor vigilance task (45% explained variance), with introverts performing better during sleep deprivation than extraverts. The only other significant result was a negative association between the Multivariate Apnea Prediction Index and the percentage of correct responses on the digit symbol substitution task (59% explained variance).

Conclusion: The link between introversion/extraversion and vigilance has been previously reported by Eysenck and others. We found that this personality trait is also associated with inter-individual variability in vigilance deficits from sleep loss, suggesting that the neurobiological mechanisms underlying vigilance performance during sleep deprivation overlap those involved in non-sleep-deprived vigilance performance. The Multivariate Apnea Prediction Index correlated with inter-individual differences in Digit Symbol Substitution Task performance during sleep deprivation, with greater apnea predictions scores corresponding to greater cognitive performance deficits. Since none of the subjects exhibited sleep apnea by polysomnographic criteria, the interpretation of this latter result remains unclear.

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Alertness and Performance in Older and Younger Adults During 16, 28, and 52 hours of Sleep Deprivation

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Introduction: As part of a study assessing the "sleep need" of older and younger individuals, we investigated their alertness and performance during sleep deprivation (SD). Previous studies have reported reduced decrements of performance and mood for older men and women (>80 years) compared with younger men (21-28 years) during 36 hours of SD, especially during times corresponding to their habitual bedtimes (Monk et al., 1992, 2000). Another study reported that young adults show significantly greater subjective fatigue and larger decrements in normalized objective performance (reaction time) than older adults during a 40-hour SD (Brendel et al., 1990). Our study explored alertness and performance for younger and older adults during a SD lasting up to 52 hours.

Methods: 23 young men and women (target 18-30 years) and 9 older men and women (target 65-85 years) were sleep deprived under constant routine conditions for 16 (4 older, 8 younger), 28 (3 older, 8 younger), or 52 hours (2 older, 7 younger). All subjects had physical exams, EKG, blood and urine tests, and clinical sleep screens before being classified as healthy and medication free. For three days before SD, subjects participated in sleep extension protocols that included 16 hrs of sleep opportunity per 24 hours. The SD began at ~1600 for the SD28 and SD52 conditions, and at ~0400 h for SD16 condition; the exact time was adjusted for each subject's habitual sleep schedule. Subjective tests included visual analogue Alertness (Alert) and Tired (Tired) scales and the Karolinska Sleepiness Scale (KSS) given every 30 minutes. Performance tests included the Digit Symbol Substitution Task (DSST) and Addition Task (ADD) administered every 2 hours. Raw subjective scores were averaged for each subject in four-hour bins throughout the SD and then averaged across subject groups. Performance scores were normalized using Z-scores and then analyzed as described above. Statistical significance was determined using repeated measures ANOVA.

Results: For most of the time awake, subjective and objective measures were similar in both age groups. Older subjects reported significantly higher levels of alertness (Alert, Tired and KSS) after 32-36 hrs awake, corresponding to ~ 0000-0400 (clock hours), and in some of the adjoining time bins during the 28 and 52 hr SD. Older subjects also had significantly better DSST Z-scores after 28-32 and 48-52 hrs awake. During the 16-hr SD, younger adults reported significantly higher KSS and lower Alert than older after 12-16 hrs awake, corresponding to ~1600-2000 (clock hours), while DSST Z-scores were significantly higher for older adults during this same time interval. ADD Z-scores showed no significant differences across time awake for either group.

Conclusion: The analysis revealed a trend in older subjects toward higher levels of alertness than younger subjects at times of expected sleepiness during SD, but similar subjective and objective measures at other times. This difference generally occurred in the evening/early morning. Performance measures showed a similar trend. These findings suggest

that underlying influences on alertness and performance may change with age and may reflect changes in homeostatic drive and/or a reduction of the circadian drive for sleep with aging.

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Age Effects on Neurobehavioral Speed Before and After Sleep Deprivation in Healthy Adults

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Introduction: It is well known that speed of neurocognitive responses undergoes slowing with age. While it is also often assumed that these effects are confined to the later decades of life, they begin well before old age. For example, professional athletes in physically demanding sports are frequently forced to retire by the third and fourth decade of life due to small changes in physical and cognitive speed. Since slowing of psychomotor reaction times (RT) and cognitive throughput (CT) are often used as markers of the effects of sleep deprivation, we sought to determine whether small age-related differences in these behavioral capabilities affected subjects' responses to sleep loss.
Methods: N=41 healthy subjects (37m, 4f, aged 21-47y) completed a 10-day laboratory protocol involving 3 baseline nights of sleep, 88h of total or partial sleep loss, and 3 recovery nights of sleep. Subjects were randomized to 1 of 3 experimental sleep loss conditions: n=13 completed 88h of total sleep deprivation; n=13 completed 88h with a single 2h nap period each day (02:45-04:45); and n=15 completed 88h with two naps of 2h TIB per 24h (02:45-04:45, 14:45-16:45). Subjects remained in the laboratory with light levels <50lx (<1lx during sleep) and ambient temperature at 24±1°C. Every 2h during wakefulness they completed a 35min computerized test battery that included the psychomotor vigilance task (PVT) and digit symbol substitution task (DSST). The PVT was used to measure fastest RT (i.e., the mean of the 10% fastest RTs on each trial), and the DSST was used to measure CT (i.e., the number of correct substitutions per unit time on each DSST). Subjects were instructed to perform as fast as possible on both tasks without making errors. Repeated-measures analysis of variance was used to compare results for two age groups: 21-29y (20s; n=28; mean age=24.5y) and 30-47y (30s; n=13; mean age=36.8y).
Results: Age-related differences were found in CT speed throughout the 27 performance trials during 3 baseline days and up to the first night of sleep loss. Both 20s and 30s subjects showed comparable performance changes due to learning and time of day over these trials ($F=7.55$, $p<0.001$), but 20s subjects consistently averaged faster CT speed than 30s subjects ($F=6.81$, $p=0.013$). PVT fastest RT also showed change over time during the baseline ($F=4.63$, $p<0.001$), and 20s subjects averaged faster RTs than 30s subjects ($F=2.65$, $p=0.11$). Sleep deprivation adversely affected both CT ($F=4.83$, $p<0.001$) and RT ($F=5.61$, $p<0.001$), but eliminated age-related differences in CT ($F=1.15$, $p=0.29$) and RT ($F=0.24$, $p=0.62$), as younger subjects (20s) experienced greater changes in CT and RT than older subjects (30s).
Conclusion: Age-related differences in cognitive and psychomotor speed were found during non-sleep-deprived periods among healthy adults in their third to fifth decades, with the advantage going to youth. Sleep deprivation slowed both RT and CT, but the effects were larger in the younger age group, resulting in loss of age-related differences in speed of performance. We are currently investigating why the age differences in baseline neurobehavioral speed appear to diminish during sleep loss.

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Dose Response Effects of Short Duration Naps During Extended Wakefulness

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Introduction: Previous research has demonstrated significant deficits in neurobehavioral functioning during periods of extended wakefulness. Strategic use of napping may be a countermeasure to reduce these deficits, but studies have not established the dose-response effects of increasing nap opportunities. This study examined the dose response effects on neurocognitive function and subjective assessments for two 2h naps per 24h, versus one 2h nap per 24h, versus no naps, during 88h of sleep deprivation.
Methods: Forty-one healthy subjects (37m, 4f, aged 21-47y) completed a 10-day laboratory protocol. After 3 nights of baseline sleep, subjects remained awake for 88h (3.7 days), followed by 3 recovery sleep periods. Subjects were randomized to receive either two naps of 2h TIB per 24h (02:45-04:45, 14:45-16:45, n=15), one nap of 2h TIB per 24h (02:45-04:45, n=13), or no nap sleep (n=13). Subjects remained in the laboratory throughout the protocol, with light levels <50lx (<1lx during sleep) and ambient temperature at 24±1°C. Every 2h during wakefulness, subjects completed a 35min computerized neurobehavioral assessment battery containing both objective tests of neurocognitive performance and subjective measures of fatigue and sleepiness. Performance on the psychomotor vigilance task (PVT), digit symbol substitution task (DSST) and probed recall memory task (PRM), as well as the KSS and POMS were compared among the three groups using repeated-measures analysis of variance (ANOVA) with baseline as a covariate. For the present report, performance bouts immediately following the nap sleep periods (which could be affected by sleep inertia) were not included in the analyses.
Results: Significant dose-related effects were evident for a number of neurobehavioral performance measures, with higher levels of performance observed in subjects allocated to two naps per 24h, followed by subjects allocated to one nap per 24h, and with the lowest levels of performance found in subjects receiving no sleep during the 88h sleep deprivation. There were main effects of time for PVT lapses ($F[36,1332]=6.33$, $p<0.001$), fatigue on the POMS ($F[36,1260]=5.86$, $p<0.001$), and sleepiness on the KSS ($F[36,1332]=2.49$, $p<0.001$). There were main effects of condition for PVT lapses ($F[2,37]=7.21$, $p=0.002$), DSST number correct ($F[2,37]=7.57$, $p=0.002$), and PRM number correct ($F[2,37]=3.07$, $p=0.058$). Significant interactions of condition by time were found for PVT lapses ($F[72,1332]=1.68$, $p=0.022$), DSST number correct ($F[72,1332]=2.77$, $p<0.001$), PRM number correct ($F[72,1332]=1.52$, $p=0.013$), and KSS sleepiness ($F[36,1332]=2.49$, $p<0.001$). There was a trend for an interaction for POMS fatigue ($F[72,1260]=1.38$, $p=0.095$).
Conclusion: Dose-response effects of even short duration (2h) naps were observed during extended sleep loss, with the greatest amount of sleep allowed per 24h producing the greatest attenuation of sleep loss-induced decreases in neurobehavioral outcomes. Although subjective assessments of fatigue did not exhibit statistically significant effects of nap sleep, measures of sleepiness and cognitive performance clearly showed beneficial effects of increasing nap frequency. These findings

suggest that strategic use of naps may be an efficient countermeasure to reduce the detrimental effects of extended sleep deprivation on cognitive functions.

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Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) Model Assessment: Individual Differences

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Introduction: In 2001, the U.S. Department of Defense Fatigue Countermeasures Working Group adopted Dr. S. Hursh's Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) model as a working model of human cognitive effectiveness based on a function of sleep factors (e.g., circadian rhythm, sustained wakefulness, sleep inertia, daylight exposure). Following APSS's 2002 annual meeting in Seattle, WA, the jointly-hosted DoD/NASA/DOT Fatigue and Performance Modeling Workshop reviewed SAFTE along with a variety of other such models and compared their ability to account for 5 different data sets. Among Workshop conclusions was that additional efforts to validate these models, especially in regard to individual differences, would be of value. This presentation is a preliminary assessment of SAFTE's ability to account for data from 36 hours sleep deprivation by natural long sleepers (LS) and short sleepers (SS).
Methods: Five LS (22.2 ±4.6 years, 4F) and six SS (38.8 ±12.2, 2F) were recruited through local media. Their characterization as LS and SS was established through telephone interview and initial 2-week recording of sleep logs and wrist-worn actigraphy. Subjects spent 4 nights in the UCSD sleep laboratory over a 2-3 week period, including an Adaptation Night, a Normal Night (NN) of sleep, 36 hours Total Sleep Deprivation (TSD), and a Recovery Night of sleep. Subjects completed the Psychomotor Vigilance Test (PVT) on a desktop computer 4 times (a baseline measurement, and at 20, 24, and 28 hours of TSD). Actigraphy data were collected a minimum of 3 days prior to and throughout TSD. These actigraphy data yielded a sleep history record that could drive SAFTE model predictions.
Results: Average bed and wake times were 00:05 (±0:44) and 09:14 (±1:00) for LS and 00:53 (±0:58) and 06:38 (±1:00) for SS. Mean sleep duration was 546.9 ±23.6 minutes for LS and 344.2 ±31.6 minutes for SS, with no significant differences in sleep efficiency (LS = 90.8 ±6.6%, SS = 90.3 ±5.8%). Performance on PVT variables (e.g., mean RT, median RT, slowest 10% RT, lapses) declined significantly for all subjects with TSD. SAFTE model predictions, derived from NTI's Fatigue Avoidance Scheduling Tool (FAST), were better than chance (e.g., for PVT mean RT, r = -.488; p = .0007) and were better than predictions of simpler models. Interestingly, with data available to date, SS performance during TSD corresponded more closely with the circadian function of the SAFTE model than did LS performance. LS performance during TSD corresponded more closely with the sleep homeostatic function of the SAFTE model. This preliminary finding is consistent with Aeschbach et al., 2003 in which it is suggested that SS may have a different circadian pacemaker program and thus could be more sensitive to circadian rhythm effects than LS. Additional data will serve to further test this preliminary finding.
Conclusion: Successful fatigue-performance modeling has obvious benefits. However, application of these models is currently limited by a need for further validation. A key unknown is how to model individual differences in susceptibility to the effects of sleep loss. The present work is a contribution to the larger modeling effort.

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Mouse Gender Differences in Sleep Regulation and Response to Restraint Stress

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Introduction: Surprisingly few studies have been conducted to examine sexual dimorphisms in the expression of sleep and its regulation. In mice, the mammalian species of choice in genetic research, such studies are lacking. Instead, only male mice have been recorded to reduce variability; and the response of female mice to experimental manipulations such as sleep deprivation and restraint stress has not yet been characterized. In this study we characterized sleep of female and male mice under baseline conditions and after sleep deprivation. To verify whether gender differences in recovery sleep after sleep deprivation were related to difference in stress susceptibility we also performed a short (1-h) restraint stress. Restraint stress has been reported to selectively promote paradoxical sleep (PS) in male mice while leaving slow-wave sleep (SWS) relatively unaffected.
Methods: Male mice (n=8) and female littermates (n=10) were implanted for chronic sleep recordings. In this report, data from 3 males and 4 female mice thus far analyzed were included. During the experiment mice were housed individually, with ad libitum access to food and water and maintained on a 12:12-h light:dark cycle. Activity was monitored via passive infrared motion detectors. One week after surgery, mice were habituated to the recording conditions for 10 days. After the habituation period, EEG and EMG were recorded from each animal for 24 h without disruption. The experiment was then carried out the following day. One experiment was carried out each week. The first experiment was a sleep deprivation of 6 h duration starting 2 h after lights-on. A restraint stress experiment began the following week one hour prior to dark onset. To control for effects of sleep loss, mice were sleep deprived for one hour prior to dark onset the following week. After each of the three experiments, recovery sleep was recorded for 24 h following the experiment. Sleep recordings were visually scored and three stages were determined: wakefulness (W), SWS, and PS.
Results: A pronounced gender difference in activity ($p<.001$) was observed, which, coupled with gender differences in sleep amount, indicates sexual dimorphism in activity per unit wakefulness. A gender difference in sleep amount was also observed. Males exhibit, on average, 13.5% more SWS across two 24-h baseline periods. Males spent 36.4% of their time in the dark period in SWS and 7.5% in PS , while females spent 21.4% of the dark period in SWS and 3.6% in PS. This overall difference in sleep amount results from the males obtaining more PS ($p<.03$) and more SWS ($p<.02$) during the dark period when compared to females in the same conditions. In the first 18 h period following the 6-h sleep deprivation, females surprisingly showed a decrease in SWS while males show the typical increase in SWS. These gender differences did not reach significance in this preliminary data set ($p<.07$) but the trend was evident. Gender difference was not found in the effect of sleep deprivation on the amount of PS in the 18 h recovery period after a 6 h sleep deprivation ($p<.12$). Following restraint stress, both males and females exhibited similar increases in the amount of PS during the 23 hour period and, as previously reported, the increase in PS after a 1-h sleep deprivation was smaller than that induced by restraint stress. In females, however, SWS increased significantly over baseline after

immobilization stress (p<.04).
Conclusion: These results indicate important sexually dimorphic changes in sleep amount and sleep regulation in mice under baseline conditions and after experimental manipulations such as sleep deprivation and restraint stress. We will also analyze changes in EEG spectra and gender differences in quantitative EEG measures such as delta power. To date, (molecular) genetic studies of sleep have been based primarily on males. By studying gender differences in sleep, much can be learned about sleep and about the validity of prior sleep genetics studies.

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The Effectiveness of Caffeinated Gum on Psychomotor Vigilance During a 30 Hour Field Study

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Introduction: The efficacy of caffeinated gum has been demonstrated multiple times in laboratory settings. The present study used a palmtop psychomotor vigilance task (PVT) in a simulated field operation with Canadian soldiers. The purpose was to test the effects of repeated administrations of caffeinated gum on performance in the field.
Methods: 30 soldiers volunteered for a field study and were randomly assigned to one of 2 groups. After obtaining 3 hours of sleep during the first night, they were awake for 30 hours, performing marksmanship and vigilance tasks, including the PVT. After 16.75 hours of continuous wakefulness (at 2145 hrs), 2 groups received 100 mg of gum, and 2 received placebo - then testing resumed. Approximately three hours later (0000), those that had received caffeine got another 200mg, and the placebo groups were administered placebo again. The caffeine group then received another 100 mg caffeine at 0200 hrs, and 200 mg more at 0400 hrs. The placebo group always received the placebo.
Results: Data were analyzed using a two-way mixed ANOVA with corrections for repeated measures. For the purpose of comparisons, only the common time points between the two groups were included. Minor lapses were defined as reaction time (RT) greater than 500 msec and major lapses are RT greater than 3000msec. Between groups, significant main effects were found for RT, Speed, Minor Lapses, and Major Lapses (F = 4.329, F=7.581, F=8.428, and F=7.806 respectively, p<.05). Across session, significant differences were found for RT, Speed, Minor Lapses, and Major Lapses (F=5.501, F=20.352, F=15.742, and F=10.303 respectively, p<.03. Likewise there were differences for the Group by Session interaction for RT, Speed, Minor Lapses, and Major Lapses (F=4.075, F=9.222, F=5.811, and F=7.438 respectively, p<.05. Specifically, the groups began to differ at 0200 hrs for RT, Speed and Lapses. There were no significant group differences in the number of errors of commission.
Conclusion: Consistent with previous findings, the PVT was found to be sensitive to sleep loss. However, group differences were not evident until after the second administration of caffeine-most likely reflecting the relatively greater combined effects of circadian rhythm and increasing level of sleep debt on performance in the placebo group. The present study verifies the sensitivity of the palmtop version of the PVT to both sleep loss and caffeine in the operational environment.

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Effects of Acute Sleep Deprivation On Cardiovascular Autonomic Modulation

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Introduction: Acute sleep deprivation (SD) has been hypothesized to trigger adverse cardiovascular events via sympathetic activation. However, studies in supine humans in SD protocols of 13 hours of wakefulness, one night of SD, and 30 hours of self-imposed SD have demonstrated generally unchanged resting plasma catecholamines, and decreased sympathetic cardiac modulation and muscle sympathetic nerve activity. This study aimed to delineate cardiovascular autonomic modulation associated with progressive SD in subjects required to function cognitively and remain out of bed.
Methods: Eighteen non-sleep deprived subjects (16 male, 2 female, 26.0±4.6 yrs, normal BMI) underwent 36 hours of total SD monitored by polysomnography and video. Precordial ECG and continuous beat-to-beat blood pressure (BP) from radial artery applanation tonometer, were obtained at 0900 on the first study night (baseline), and every 12 hours of SD thereafter. Subjects remained upright, prior to each measurement period. Each period consisted of: 15 minutes supine, 15 minutes sitting upright, and, sitting, performing three consecutive nonverbal recognition tests covering basic vigilance to working memory storage and executive function (10-minutes each). Fourier transforms of low frequency (LF, 0.05 to 0.15 Hz), and high frequency (HF, >0.15 to 0.40 Hz) oscillatory components of heart rate variability (HRV) and the LF component of BP variability (BPV) were computed, expressed in normalized (n) units ([total power of the components]/[total power-very low frequency power]) x 100. HF power reflected cardiac parasympathetic modulation; the LF component of HRV, cardiac sympathetic modulation. The LF power-HF power ratio of R-R variability (LFR-R/HFR-R) reflected sympatho-vagal balance. Sympathetic control of the microcirculation was assessed as LF modulation of BP (BPLFN). Physiologic measures were averaged over 3-5 minutes of the last portion of each condition.
Results: Supine, heart rate (HR, bpm) was significantly lower at 12 (58.2±6.3) and 36 hours (56.9±7.1) of SD than during nocturnal non-SD baseline (62.1±9.0), or at 24 hours (62.7±9.0) of SD. No significant differences in BP from baseline through SD were found. Sitting, HR increased at 24 hours of SD, with no significant changes in BP from baseline. There were no significant changes in HRV during SD supine. Sitting, HRV LF(n) increased significantly from baseline (59.39±15.65%) to 12 (66.98±13.90%), 24 (66.80±11.51%), and 36 (65.86±11.97%) hours of SD, as did LFR-R/HFR-R (baseline 2.66±1.74 to 3.84±2.33, 3.44±1.94, 4.09±4.56). HRV HF(n) decreased from baseline to 12, 24, and 36 hrs of SD (29.03±11.57% to 22.81±10.36%, 23.77±8.71%, 23.55±9.19%). BPV LF(n) increased significantly at 12, 24, and 36 hrs of SD supine (63.20±16.48% to 72.44±13.16%, 74.38±14.18%, 75.70±14.14%) and sitting (all significance p<.05 by ANOVA). Autonomic parameters during cognitive tasks were similar to non-task values. Cognitive performance progressively declined through SD.
Conclusion: Twelve hours of nocturnal acute SD is associated with increased sympathetic cardiovascular modulation at rest and during cognitive tasks in normal humans, particularly seated vs supine. SD to 36 hours does not significantly change 12 hour SD autonomic modulation. BP is not increased in this setting. Autonomic modulation during cognitive tasks remains similar to non-task conditions even as cognitive performance declines.

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The Assessment of Cognitive Workload Associated With Simulated Steering Task Performance: Effects of Prolonged Wakefulness and Task Demand

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Introduction: It has been proposed that early detection of driver drowsiness may be enhanced by assessing driver status using measures of cognitive workload. In the present study, three validated measures of workload, including secondary task performance, the amplitude of the 0.1 Hz component of heart rate variability, and self-reported ratings, were investigated for their sensitivity to independent changes in driver sleepiness and task demand.
Methods: Participants were 24 healthy male university students (mean age = 19.3 years) who completed testing sessions on two separate nights, at 2030 and 0430, respectively, in a counterbalanced order. During each session, a computerized visual tracking task was performed that required participants to use a steering wheel to keep a target inside a set of moving parallel lines. Task difficulty was manipulated by varying the distance between the lines. Testing sessions consisted of three consecutive 12-minute trials in which the tracking task was completed under differing conditions of demand (Easy, Moderate, Difficult) in a counterbalanced order. A secondary serial addition task was performed during six minutes of each trial and served as a behavioural measure of workload. The 0.1 Hz component of heart rate variability was derived from power spectral analysis of inter-beat interval data collected throughout each trial. Following each trial, the Stanford Sleepiness Scale, and visual analogue scales assessing self-reported workload were completed.
Results: Repeated-measures ANOVAs were performed with Time of Night and Task Demand extracted as sources of variance. The number of steering task errors increased with Time of Night ($F(1,18) = 15.13$, $p = .001$) and as a function of Task Demand ($F(2,36) = 153.62$, $p < .001$). A significant interaction indicated that steering performance deterioration was greatest under the Difficult condition and least under the Easy condition ($F(2,36) = 14.86$, $p < .001$). Measures of workload were all sensitive to changes in Task Demand. As demand increased, serial addition errors increased ($F(2,36) = 4.66$, $p < .02$), relative 0.1 Hz power decreased ($F(2,34) = 4.81$, $p < .02$), and self-reported workload increased ($F(2,36) = 28.38$, $p < .001$). However, only self-reported workload increased as a function of Time of Night ($F(1,18) = 12.96$, $p < .01$) and there were no significant interactions between Task Demand and Time of Night for any of the workload measures. Stanford Sleepiness Scale scores, on the other hand, were sensitive to Time of Night ($F(1,18) = 91.02$, $p < .001$) but did not vary significantly with changes in Task Demand.
Conclusion: In the present study, measures of cognitive workload were sensitive to variations in the amount of demand associated with the steering task. However, prolonged wakefulness did not reliably induce changes in workload. Measures of sleepiness displayed the opposite pattern of results. These findings suggest that measures of cognitive workload and sleepiness represent independent constructs and should not be used interchangeably to assess driver drowsiness.

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Repeated Administrations of Caffeinated Gum and the Effects on Psychomotor Vigilance During Sustained Wakefulness

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Introduction: Previous research has studied the effects of repeated administrations of caffeine, in a gum formulation, on a pc-based psychomotor vigilance task (PVT). Recently, a similar task has been developed at Walter Reed Army Institute of research which runs on any personal data assistant (PDA) using the Palm operating system. This was a laboratory based simulated field study conducted at DRDC-Toronto, to determine the effect of repeated doses of caffeine, during a period of sustained wakefulness, on psychomotor vigilance.
Methods: 18 Canadian reservists (17m/ 1f; mean age 26.4yrs) volunteered to undergo 30 hours of continuous wakefulness. They were assigned to the caffeine and placebo groups in a double-blind fashion, completed one run Monday through Thursday of the first week and coming back the following Monday for the other condition. During this time they received a total of 600 mg of caffeinated gum over 7.5 hours - 400mg at 2130 on Day 2 and 100mg at 0300 and again at 0500 on Day 3. Throughout the wake period, subjects completed simulated marksmanship tasks, sand bag piling, an oculomotor task, cognitive tasks, runs to exhaustion, and the Palm-PVT.
Results: The data were analyzed using a two-way mixed ANOVA, with corrections for repeated measures. Post hoc comparisons were conducted when appropriate. Minor lapses were defined as reaction time (RT) greater than 500msec and major lapses are RT greater than 3000msec. Significant main effects were found for Group, Session, and the Group by Session interaction for RT ($F=10.45$, $F=13.95$, and $F=4.19$ respectively, $p<.006$), Speed ($F=6.49$, $F=20.2$, and $F=4.13$ respectively, $p<.02$), and Minor Lapses ($F=10.51$, $F=16.82$, and $F=4.09$ respectively, $p<.004$). For Major Lapses, a significant main effect was found for Group only ($F=6.3$, $p<.02$). Post hoc comparisons found that group differences began after 19.5 hours of wakefulness and continued to the end of the study.
Conclusion: The PVT has previously been shown to be sensitive to the effects of sleep deprivation as can be seen by an increase in reaction time and lapsing, and a decrease in speed. This study showed that a 5-minute Palm-held psychomotor vigilance task version yield comparable results,and may therefore be nearly as sensitive,as the 10-minute PVT that has been used previously in the laboratory studies. Further analyses will focus on correlation of Palm-PVT findings with findings from operationally relevant tasks like marksmanship and physical endurance.

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An Analysis of the First Night Effect on REM Sleep EEG Coherence

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Introduction: EEG coherence reflects functional interregional-coupling. Having to sleep for a first night in a laboratory induces disorders of sleep that may also be reflected in altered EEG patterns. The aim of this study was to analyze the first-night effect on measures of interhemispheric EEG coherence during REM sleep, a state of endogenous CNS

activation, in young healthy adults.
Methods: Ten healthy participants (5 men, 5 women, aged 21.4 +/- 4.9 years) were recorded for two consecutive nights in a sleep laboratory. All were free from sleep disorders and from a personal or a familial (first degree) history of psychiatric or neurologic disorders. Subjects were asked to keep a regular sleep-wake schedule for 14 days before coming to the laboratory. Napping was not allowed on days prior to recordings. Both nights were scored according to Rechtschaffen & Kales (1968). EEG was recorded using a set of 10 electrodes (Fp1, Fp2, F7, F8, C3, C4, O1, O2, T3, T4) referred to linked earlobes. Twenty-four 4?seconds artefact free epochs equally distributed throughout the first three REM sleep periods were selected. EEG samples were submitted to Fast Fourier Transform with a resolution of 0.25 Hz and a cosine window smoothing. Power amplitude was extracted and coherence analysis was performed on eight frequency bands: Delta (0.75-3.75 Hz), Theta (4.00-7.75 Hz), Alpha-1 (8.00-10.00 Hz) Alpha-2 (10.25-12.75 Hz), Sigma (12.00-14.00 Hz), and Beta (13.00-20.25 Hz). Cross-spectrum and auto-spectrum estimates of each electrode were calculated with a dedicated software (Harmonie, Stellate Systems, Montreal). Night 1 and night 2 magnitude of coherence function (expressed as intervals in %) for all interhemispheric pairs of recording sites was compared on each frequency band using paired t-tests.
Results: Sleep architecture showed a typical first night effect, with longer sleep latencies, increased number of awakenings, and decreased total sleep time. Compared to night 2, coherence analysis of the EEG revealed that night 1 was associated with significantly higher Alpha-2 coherence at T3-T4 (4.8 +/- 2.5 vs. 2.8 +/- 1.5) and significantly lower Delta coherence at O1-O2 (38.9 +/- 3.2 vs. 41.2 +/- 2.2).
Conclusion: These results show that REM sleep EEG coherence is sensitive to the first-night effect in young healthy adults. The fact that a circadian-dependant EEG band (rapid Alpha) and a sleep homeostasis-dependant EEG band (Delta) were both affected by the first-night effect warrants further research.

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The Effect of Caffeinated Gum on Psychomotor Vigilance in High Versus Low Caffeine Consumers

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Introduction: Previous research has shown that caffeinated gum improves cognitive performance during sleep loss faster than caffeine in pill form, and that performance can be sustained with repeated administrations. One remaining question is whether caffeine is differentially efficacious in habitually high versus low caffeine users.
Methods: Sixteen volunteers (7 f/ 9 m, mean age = 26.6 yrs) were recruited and assigned, in a Latin square design, to 100, 200, or 300 mg of caffeine or placebo. Each group of four volunteers came to the laboratory once a month for four months for a different dose. They underwent 27 hours of continuous wakefulness, being repeatedly tested on several cognitive tasks including the Psychomotor Vigilance Task (PVT).
Results: Data were analyzed using two-way mixed ANOVAs, with corrections for repeated measures. Post hoc comparisons were done when appropriate. Significant differences were found for Group, Session, and the Group by Session interaction for Speed (F=10.51, F=19.65, and F=2.22 respectively, p<.003), and Lapses > 1sec (F=9.89, F=15.88, and F=2.03 respectively, p<.004), Lapses > 3seconds (F=15.96, F=15.48, and F=2.31 respectively, p<.001) and Lapses >5 seconds (F=20.5, F=16.08, and F=4.11 respectively, p <.000). More specifically, simple main effects were significant for all groups across sessions, and for sessions occurring between 20.5-25.5 hours awake among all groups. Most importantly, within each dose, there were significant differences between the high and low caffeine users. Analyses of slopes showed that even in the two highest caffeine doses, those that were low users continued to improve with each administration whereas the performance of those who were high users continued to degrade.
Conclusion: As has been found in the past, repeated administrations of a caffeinated gum was able to ameliorate the effects of sleep deprivation, with the higher doses being more efficient at consistently sustaining performance. It was also found that there was a difference in the efficacy of caffeine for this purpose in habitually high versus low caffeine users. Those volunteers who habitually consume >400 mg caffeine per day required higher doses of caffeine to sustain performance than did those who habitually consume < 100 mg caffeine per day.

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Sleep Deprivation Reduces The Number Of Newly Generated Neurons In The Dentate Gyrus Of The Hippocampus Of The Adult Rat

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Introduction: The subgranule cell layer (SGZ) in the dentate gyrus (DG) of the adult hippocampus contains progenitor cells, which have potential to differentiate into neurons. The maturation of newly-generated cells into functional neurons occurs over a period of three weeks. Several factors are known to affect the proliferation of new cells in this region. Recently we reported that 4 days of sleep deprivation (SD) reduced proliferation of new cells in the SGZ of the DG and that this effect is not due to nonspecific stress, or the forced locomotion used to produce SD in our paradigm. Now we present data indicating that SD reduced the number of new cells expressing a mature neuronal marker (NeuN) three weeks after a 4 days period of SD.
Methods: Adult Male Sprague-Dawley rats (300 g) were implanted for polysomnographic recording. Rats were divided into treadmill sleep deprived (SD), and treadmill control (TC) groups. SD and TC rats were kept for 96 h on a treadmill that moved either for 3 sec on/12 sec off (SD group) or 15 min on/60 min off (TC group) to equate total movement but permit sustained rest periods in TC animals. The thymidine analog 5-bromo-2-deoxyuridine (BrdU) was injected after the first 48 h of the experimental procedure in both groups (50 mg kg-1, i.p.); experiments continued for an additional 48 hours period. Following the 96 h of experimental manipulations rats were allowed to survive for three weeks before the phenotype of BrdU-positive cells in the DG was assessed. Brains were processed for BrdU/NeuN double labeling performed on every twelfth free-floating section and analyzed by laser confocal microscopy. A total of 12 sections were analyzed in 4 SD and 4 TC rats.
Results: Preliminary analysis showed that after three weeks the number of BrdU-stained cells was reduced compared to control (5297 +/- 171.47 TC and 3401 +/- 130.77 SD, p < 0.05). Regarding the phenotype of cells, the percentage of BrdU-labeled cells expressing NeuN was 45% lower in the SD group in comparison with the TC group.
Conclusion: These results show that SD reduces the number of newly generated hipocampal cells that express a neuronal phenotype after 3 weeks.

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Epworth Sleepiness Scores In Medical Residents

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Introduction: Because of the interest in and the importance of having alert residents as demonstrated by the new ACGME resident work requirements, and concern generated when we obtained Epworth Sleepiness Scale (ESS) scores from a small convenience sample of residents with a mean score of well over 10, we systematically obtained ESS scores of those entering and completing residency programs at Eastern Virginia Medical School (EVMS). We hypothesized that if their schedule increased their sleepiness, those entering would be less sleepy and have lower ESS scores than those completing their residency programs.
Methods: During the past year, 83 Eastern Virginia Medical School (EVMS) students entering postgraduate education programs (85% of the total) and 45 students exiting postgraduate education programs (57% of the total) completed the Epworth Sleepiness Scale. The entering residents represented 17 medical training and fellowship programs. The exiting residents represented 15 medical clinical training and fellowship programs. Men accounted for 53 of the respondents and women accounted for 73 of the respondents. Mean age (+- standard deviation) of those entering was 30 (+-4.5) years and of those exiting was 32 (+-4.0) years. The mean number of years in the program of those exiting was 3.6 (+-1.2).
Results: Over all residents, the mean (+ SD) of the EES score was 8.6 +-3.9. Those entering (8.1 +-3.6) were less sleepy than those exiting (9.6 +-4.5) the programs ($F = 6.4$, $df = 1/121$, $p = 0.013$). Of those exiting, 51% had ESS scores of 10 or more (range = 0-22). Of those entering, 29% had ESS scores of 10 or more (range = 0-18). There was no significant difference between men and women. Age did not significantly correlate with the EES score. There was a tendency for men and older residents to have lower ESS scores ($p < 0.1$).
Conclusion: Residents leave their training programs sleepier than when they began. Presumably, they accumulate a sleep debt and do not accommodate to interrupted and restricted sleep schedules. However, the exiting residents were less sleepy than those in our convenience sample of residents. Possibly those about to leave had a better schedule toward the end of their training program. The ESS scores indicate that even some entering residents have sufficient sleepiness to impair their performance. Therefore, monitoring the EES scores of residents scores, making them aware of the results and implications, and offering a session with a sleep knowledgeable professional may benefit the residents and the training program.

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The Effect Of REM Sleep Deprivation On A Progressive-Ratio Task And Monoamine Levels Within The Brain

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Introduction: We have previously shown that short-term REM sleep deprivation (RSD) by the flower-pot method does not facilitate normal acquisition or maintenance of an operant task and furthermore, RSD animals show a within-session decline in responding similar to that shown by animals that have been dopamine-depleted. These findings suggest that RSD animals have a decreased motivation for food reward possibly due to a deficient capacity for work effort. These experiments sought to determine whether RSD rats would be impaired in a task that primarily measures work effort, the progressive ratio task, and investigated monoamine levels within brain regions involved in motivated behaviors.
Methods: Sleep Deprivation: The flower-pot method was used to deprive rats of REM sleep (D rats). They were compared to large platform controls (C rats) and a home cage control group (H rats). Behavioral Testing: Animals were trained up to a progressive-ratio 2 (PR2) schedule in which the rat was reinforced for the first press, and then had to increase responding by two lever presses for each subsequent pellet. Following training, rats were assigned to D, C, or H groups and tested on the PR2 operant task each of the 5 days of RSD. In experiment 1, animals were kept food deprived during testing and in experiment 2 animals were fed ad-lib after acquiring the task. High Performance Liquid Chromatography (HPLC): HPLC with a ESA MD-150 (RP-C18) column (150 X 32, 3m) was used for quantification of NE, 5-HT, DA, and their metabolites. The mobile phase was an aqueous solution of 0.1M sodium phosphate, 50mM citric acid, 10% acetonitrile with a pH of 3.01. The flow rate was 0.50 ml/min. Compounds were oxidized at 300 mV.
Results: Both progressive ratio experiments showed similar results; the most robust group differences, however, were observed when the rats were free feeding. From day 2 onwards of RSD, the free-feeding D rats exhibited a significantly lower break point than the H controls ($p < 0.05$). Furthermore, dopamine and DOPAC levels were increased in D rats compared to H controls in the nucleus accumbens ($p < 0.05$) but not in the medial prefrontal cortex, suggesting that this difference maybe site specific. Furthermore, the DOPAC/dopamine ratio was decreased in D rats compared to H controls ($p < 0.05$) suggesting a possible decrease in turnover of dopamine within the nucleus accumbens.
Conclusion: These results suggest that RSD produced by the flower-pot method impairs work effort or motivation for food reward despite leading to increased appetite in free-feeding situations. These data are similar to reports of a decrease in work effort in rats that have received dopamine depletions or administration of dopamine antagonists. In fact, the HPLC analysis reveals that RSD rats have decreased DOPAC/dopamine ratios in the nucleus accumbens in comparison to H controls, suggesting that behavioral effects of sleep deprivation may be related to dysregulation of dopamine systems. Future experiments include an attempt to recover this decline in exerted work effort observed in RSD rats with dopamine agonists.

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Sleep Patterns Of Incoming Cadets At The United States Military Academy

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Introduction: This project is part of a longitudinal study of sleep patterns of US Military Academy Cadets over a four-year period. Research has shown that the sleep requirements of adolescents and young adults are distinctly different from those of other age groups. The circadian fluctuation of melatonin differs in these groups and is thought to contribute to the underlying processes that control sleep patterns. In adolescents and young adults, melatonin is released later than in pre-teens and adults. Consequently, this population tends to go to bed later, but is less able to wake up early in the morning. Under these conditions, human

performance is likely to be degraded in both academic and military settings. This study will be a test bed for examining sleep and performance in the Army's Objective Force/Future Soldier program.

Methods: Baseline survey data were obtained on a nearly 1300 new Cadets, all members of the Class of 2007. The data examined sleep patterns for the 30 days prior to reporting to USMA. Actigraphy data were collected on a randomly-selected sample of 80 New Cadets through Cadet Basic Training (CBT), an 8-week orientation to the military before classes begin in the Fall semester. Additional data were collected on a sample of 40 USMA Cadre upperclass Cadre members who interact with the incoming Cadets during the CBT period. Wrist Activity Monitors (WAMS) were used to assess sleep quality and quantity. This technique has been widely used in studies of sleep and the assessment methods and supporting software are readily available.

Results: Results demonstrate that incoming Cadets report receiving a mean of 8.39 hrs of sleep (SD = 1.62) for the month prior to reporting to USMA. During CBT, the average amount of sleep dropped to 4.9 hrs (95% CI = 4.4-5.4). For the upperclass Cadre members, the amount was 5.0 hrs (95% CI = 4.8-5.2).

Conclusion: This study represents the first phase of a comprehensive study of sleep and circadian rhythms of the future leaders of the armed services. The average Army Cadet received about 5.0 hours of sleep during Cadet Basic Training, approximately four hours less than the literature states is optimal for young adults in this age group. This amount is over three hours less than what Cadets received prior to their arrival in West Point. Similar sleep patterns were seen in participating upperclass Cadre members during CBT.

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Effects Of Migration On Cognitive Performance In The White-crowned Sparrow (Zonotrichia leucophrys gambelii & Zonotrichia leucophrys nuttalli)

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Introduction: We have established that migratory songbirds like the White-crowned Sparrow (Zonotrichia leucophrys gambelii) exhibit reduced amounts of sleep for prolonged periods of time during the migratory season. Sleep deprivation, including partial sleep deprivation, has detrimental effects on cognitive performance in people and animals. To determine whether chronic sleep reduction during migration produces similar behavioral deficits, we monitored the complex operant behavior of sparrows during the migratory and non-migratory seasons, as well as after an acute episode of sleep deprivation.

Methods: Migratory sparrows (Z .l. gambelii) and a related subspecies that does not migrate (Z. l. nuttalli) were collected from Alaska and California and brought to Wisconsin. Eight birds of each subspecies were trained to respond under a multiple schedule of repeated acquisition and performance. In the repeated-acquisition components, subjects acquired a different three-response sequence each session under a second-order fixed-ratio 3 schedule. In contrast, in the performance components, subjects responded on the same three-response sequence each session under the same schedule of reinforcement. Sparrows were tested from January 2003 through December 2003. Activity levels in the home cage were monitored using infrared motion detectors. The amount of active time during the hours between 21:30 and 04:00 was used to select two 6-week periods when the birds were migrating (Spring and Fall) and two 6-week periods when they were not migrating (Winter and Summer). Birds were also deprived of sleep for one night while they were not migrating by experimenters who entered the housing room every 3 to 5 min for a 24-h period. Cages were lightly tapped if needed to keep birds awake. Responding during the migratory seasons was compared with responding during the time when birds were undisturbed and not migrating. These changes were also compared to the changes that occurred on the days before and after one night of sleep deprivation. Significant differences in response rate or accuracy of responding were associated with $p<0.05$.

Results: Experimenter-induced sleep deprivation decreased the number of responses for each subspecies in the learning components and, in the migratory subspecies, in the well-rehearsed performance components. Accuracy was unaffected. Video records did not show sleep during the testing sessions. In contrast, responding in the learning components increased significantly during the migratory season in the migratory subspecies only. There was also a significant difference between responding in the migratory and non-migratory seasons in the non-migratory Z. l. nuttalli subspecies, but in the opposite direction (i.e., the birds that did not migrate actually decreased their response rates at the same time that migrating birds increased their response rates). There were no significant changes in accuracy.

Conclusion: An acute episode of sleep deprivation impaired responding in a cognitive task in both non-migratory and migratory sparrows (while they were not migrating), as it does in other animals. In contrast, responding on the same cognitive task actually improved in the migratory species during migration, despite substantial sleep reduction. Prolonged sleep reduction during migration does not produce the same impairment in performance as seen in response to sleep deprivation.

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N1 Changes in Event Potentials Over Time During 36 Hour of Total Sleep Deprivation and Following Recovery Sleep

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Introduction: The extent of information processing is much affected by sleepiness. Event-related potentials (ERPs) are often used to provide a measure of information processing in the absence of a behavioural response. In particular, the N1 component, a negative auditory ERP peaking between 80 and 150ms, has been proposed as the electrophysiological marker of a type of "general" conscious awareness of the external stimulus. N1 amplitude gradually becomes reduced during the transition from a waking, conscious state to one of sleep and unconsciousness. A reduction in N1 has also been reported in the waking participant following slow wave sleep deprivation. In addition, N1 latency during sleep-wake transition is increased compared to pre-sleep wakefulness. Such results indicate that N1 is sensitive to brain deactivation during the sleep-wake transition. However, it is not clear whether this effect is due to sleep deprivation or sleep inertia. The present study of the effects of 36 hours of total sleep deprivation (TSD) on the N1 ERP component controlled for sleep inertia.

Methods: Three men and 8 women (age range 18 to 26) were sleep deprived for 36 hr. EEG was recorded from Fz, Cz and Pz. EOG was also recorded to monitor blink artifacts. An auditory oddball task was administered at different times in order to evaluate ERP changes over time (i.e., immediately after waking up (0hr), after 6 hr, 12 hr, 18 hr, 24 hr, 36 hr of TSD, and one hour following a single night of recovery sleep). The participant heard a frequently occurring 1000 Hz standard stimulus. At odd and unpredictable times, this was changed to either a 2000 Hz target or an environmentally novel sound. The participant's task was to detect the 2000 Hz target. This study examines the effects of TSD on the amplitude and latency of N1, as measured by the standard stimulus.

Results: N1 amplitude did not significantly differ between 0, 6, 12, 18, 24, and 36 hr of TSD, $p>.05$. However, N1 amplitude after recovery sleep was significantly smaller than at 0hr, and 36 hr of TSD, $p<.05$.

Similarly, N1 latency did not significantly differ between 0, 6, 12, 18, 24, and 36 hr of TSD, =, p>.05. However, latency after recovery sleep was significantly shorter than latency at 36 hours of TSD, p<.05.
Conclusion: These results may indicate that N1 is more sensitive to sleep inertia than to sleep deprivation, as evidenced by a significant change in amplitude and latency after recovery sleep compared to 36 hr of sleep deprivation. The decrease in N1 latency found after recovery sleep may indicate that conscious awareness processes are more rapid after sleep, despite the fact that neuronal recruitment is lower at this time.

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Long Term Synaptic Plasticity is Impaired in Animals Made Insomniac with Lesioned Ventrolateral Preoptic Nuclei

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Introduction: The impairment of memory function in nearly every model of sleep deprivation suggests that the hippocampal formation may be sensitive to the physiological effects of sleep deprivation. To examine the cellular basis for this change in memory we explored changes in hippocampal cellular functions in an in vitro slice preparation. As the experimental model for chronic partial sleep deprivation we used animals with the ventrolateral preoptic (VLPO) area lesioned. Animals with this cell-specific lesion have more than 50% total sleep loss and rarely achieve the deeper stages of delta sleep. This condition persists for more than 12 weeks, providing a model for studying chronically increased homeostatic sleep pressure without stressful external intervention.
Methods: Experiments were conducted on hippocampal in vitro slices from 1) animals 10 week post bilateral VLPO lesion (≥ 80% of cell loss) that had shown at least a 50% decrease in total sleep, and 2) control animals, matched for age. Slices were recorded while maintained fully submerged and perfused (2ml/min) with oxygenated artificial cerebrospinal fluid at 35C. Field excitatory postsynaptic potentials (fEPSPs) were recorded in the stratum radiatum of the CA1 region, using an Axoclamp-2A amplifier and were evoked by stimulating the Schaffer collateral pathway. The fEPSPs were quantified as the slope of the initial phase of the fEPSP. Long term potentiation (LTP) was induced by 2 trains of 100 stimuli at 100Hz.
Results: We found that in VLPO-lesioned animals that had lost more than 50% of total sleep the fEPSPs recorded in vitro were under a greater inhibitory tone by endogenous adenosine compared to the control animals. In slices prepared from control animals 100nM 8-cyclo-pentyl-theophylline (CPT), an adenosine A1 antagonist, increased the fEPSP slope by 49.7 ± 17.6% (n=2) compared to 196 ± 103% increase in the slices from the VLPO-lesioned rats (n=2) p≤0.01. The resulting increase of fEPSP slope upon the addition of the adenosine A1 antagonist was taken as a measure of the tonic inhibition of the synaptic transmission produced by endogenous adenosine in the slice. These observations were consistent with increased tissue adenosine levels in the hippocampus from VLPO-lesioned animals. In addition, we found that in hippocampal slices prepared from those animals the induction of LTP in the CA1 region was impaired. The mean increase in the fEPSP slope in the 30 minute period after tetanization in the control animals was 57.1% (n=3), compared to a mean increase of only 19.6% in the VLPO-lesioned animals (n=2).
Conclusion: In agreement with previous reports showing that sleep deprivation induces adenosine accumulation in the hippocampal formation in vivo and in vitro, we found that in hippocampal slices from VLPO-lesioned animals the levels of endogenous adenosine were higher compared to control animals. In addition, in these animals the induction of LTP was impaired. Since adenosine has been shown to reduce LTP in the CA1 region, we hypothesize that accumulation of adenosine may play a role in the reduction of long term synaptic plasticity in VLPO-lesioned animals.

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Validation Of A Self-Reported Method Of Measuring Sleep Deprivation

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Introduction: Recently, Propper and her colleagues suggested that sleep deprivation could be measured using people's self–reports with the following formula: sleep deprivation = sleep duration needed - typical sleep duration.
Methods: We attempted to validate this formula using the following procedures. First, we used responses of 653 male and 864 female undergraduates to a questionnaire that included items required to compute "sleep deprivation" using this formula. The difference between the means for men (1.80 ± 1.49 hrs.) and women (1.78 ± 1.17) wasn't significant (t(1515) = .29). Next, using responses of 1,306 of these students, (i.e., students who classified themselves as either Afro-Americans, Asians, Caucasians, Pacific Islanders, Mexican-Americans, or Other Hispanics), we tested for ethnic differences in "sleep deprivation" and found none (for sex F1, 1294 = .15; for Ethnicity F5, 1294 = 3.20; and for the Sex by Ethnicity Interaction F5, 1294 = 1.37). Next, from the entire sample of 1,517 undergraduate students, we computed "sleep deprivation" norms. Using these norms, we identified groups of students who scored in the top 20% (i.e., > 2.00 hrs.) and in the bottom 20% (i.e., < .00 hrs.) of "sleep deprivation." From each of these groups, we selected 50 men and 50 women who were high and 50 men and 50 women who were low in "sleep deprivation." These High and Low Groups were matched as closely as possible for age, ethnicity and year in college. Finally, using these groups, we compared responses to three scales that we felt should be sensitive to their self-reported differences in "sleep deprivation." The scales included the Stanford Sleepiness Scale (SSS), the Epworth Sleepiness Scale (EPW), and the Coren Insomnia Scale (CIS). The means and standard deviations for the High and Low Groups for each of these scales are in the table. Also in this table are the results of the t statistics computed to test the differences between the High and Low Groups for each sleep scale.
Results: High Group Low Group Sleep Scale M SD M SD t p est.w2 SSS 3.31 1.45 3.03 1.45 1.33 n.s. .004 EPW 10.01 4.34 8.26 3.68 3.07 <.001 .040 CIS 20.55 5.57 15.32 6.17 6.30 <.001 .156 The SSS is a widely used instrument for measuring an individual's current level of sleepiness on a seven–point scale. The nonsignificant difference between the High and Low Groups for current sleepiness don't support the validity of Propper's Formula as a method of measuring acute "sleep deprivation." The EPW is a well–established scale commonly used to measure an individual's propensity to experience sleepiness on a four-point scale in eight situations most people experience every day (e.g. sitting and reading; watching TV). The results suggest to us that persons who perceive the need for two or more hours of sleep per day are also more likely to perceive sleepiness in a variety of everyday activities. Finally, the results in the table for the CIS appear to provide a degree of validation for Propper's Formula in that these data suggest that persons who are high in perceived "sleep deprivation," score high in perceived

insomnia. However, an analysis of the responses to each of the individual items on the CIS revealed no statistically significant differences between the High and Low "Sleep Deprived" Groups on items that we specifically related to parameters of sleep, that are associated with insomnia, e.g., delayed sleep onset; awaken during the night; experiencing restlessness, and awakening early. Rather, the significant and meaningful difference between the High and Low Groups for the CIS is due primarily to a set of CIS items which reflect a more general self–perceived need for sleep, e.g., sleep satisfaction, the need for more sleep, and feeling rested in the morning.
Conclusion: Thus, we conclude that Propper's Formula doesn't provide a measure of sleep deprivation but rather, it seems to measure an individual's self–perception of the chronic level of sleep desired.

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Sympathetic Tone Alters Metabolism Following Sleep Deprivation
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Introduction: Recent clinical studies have demonstrated that sleep deprivation in young adults alters metabolism. Mechanisms underlying this phenomenon remain undefined; however, the increase in sympathetic activity associated with sleep loss could offer one explanation. Therefore, we have utilized two sleep deprivation paradigms to test the hypothesis that an increase in autonomic activity modifies metabolic and endocrine regulation following sleep loss in rodents.
Methods: One day before sleep deprivation, body mass and food intake were recorded in male Sprague-Dawley rats (n=28). Blood was collected for baseline concentrations (Baseline) of glucose, insulin, leptin, and free fatty acids (FFA), and a glucose tolerance test was administered to assess insulin sensitivity. Animals were then randomly divided to undergo sleep deprivation (SD) by forced locomotion in a slowly rotating wheel (1rpm) (n=10) or by gentle handling (n=10). To assess the impact of sympathetic activity following sleep loss, a subset of animals (n=8) in the gentle handling group were sympathectomized by administering 6 hydroxydopamine (100mg/kg,i.p.). Sleep was restricted by their respective technique to 4 hours of sleep. Following 4 hours of recovery sleep and fast, animals were subjected to the same metabolic assays outlined previously. Data are reported as mean±sem, and a t-test was performed to determine if differences between baseline and SD were significant ($p<0.05$).
Results: Following 20 hours of sleep deprivation using forced locomotion, there was a significant decrease in leptin (Baseline 2.18±0.42ng/mL v. SD 0.62±0.11ng/mL, $p=0.001$) and increase in FFA (Baseline 0.367±0.058mmol/L v. SD 0.556±0.077mmol/L, $p<0.05$). Interestingly, body mass decreased (Baseline 362±15g v. SD 350±13), while food intake increased (Baseline 20.8±1.2g v. SD 26.6±2.0g, $p<0.05$). This negative energy balance was reflected by the glucose tolerance test that showed decreased insulin secretion in response to the glucose load suggesting enhanced insulin sensitivity. Sleep deprivation by gentle handling resulted in alterations in concentrations of leptin and FFA that were similar to those measured using the slowly rotating wheel. Surprisingly, glucose and insulin levels in animals sleep deprived by gentle handling were further significantly diminished at each time point tested when compared to the animals sleep deprived using forced locomotion. In sympathectomized animals, sleep deprived values of glucose, insulin and leptin were normalized to their respective baseline values.
Conclusion: The alterations in insulin sensitivity and glucose utilization that were observed in sleep deprived animals by forced locomotion could be the result of exercise. However, these changes did not appear to be due to an exercise effect since animals that were subjected to sleep deprivation by gentle handling exhibited analogous metabolic and endocrine profiles. Our findings suggest that these modifications are the result of increased sympathetic activity in sleep deprived animals since effects were blocked by sympathectomy. Future studies are designed to investigate whether the activation of sympathetic tone associated with sleep loss results in increased non-insulin dependent glucose disposal in skeletal muscle and adipose tissue, and to identify which adrenergic system is responsible for mediating the effects of sleep loss on metabolism.

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Effects of Sleep Deprivation by the Disk over Water Method in Pigeons
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Introduction: Total sleep deprivation in rats by the disk-over-water (DOW) technique elicits a syndrome consisting of increased energy expenditure, debilitated appearance, skin lesions, changes in thermoregulation and eventual death. The underlying mechanisms for this sleep deprivation syndrome are unknown. Nor is it known whether the syndrome is specific to mammals or even to rats. Birds, like mammals, show distinct episodes of slow-wave sleep and REM sleep. We have performed prolonged sleep deprivation in pigeons using the disk-over-water method.
Methods: The DOW apparatus was adapted for pigeons by increasing the depth of the water to nine cm. Twelve pigeons were instrumented for recording EEG from left and right hemispheres, EOG and EMG. Birds were implanted with subcutaneous transponders in order to record body temperature. Birds were allowed to recover from surgery and were habituated to the apparatus prior to obtaining baseline sleep recordings. Weight, food, water consumption and, in 8 birds, subcutaneous temperature, were recorded every day throughout the experiment. The birds were deprived of sleep for up to twenty-nine days. Following the sleep deprivation, the pigeons were allowed up to seven days of recovery during which they remained in the DOW apparatus and EEG recordings were continued. One day of baseline, the last day of deprivation and the first day of recovery were scored by a combination of video image and EEG.
Results: There were substantial increases in total sleep and REM sleep on the first recovery day compared to baseline amounts for the Deprived pigeon. Scoring on the final day of deprivation showed 40% of baseline SWS and 10% of baseline REM. Food intake and body weight changes were more equivocal. Deprived and Control birds increased energy expenditure whereas energy expenditure fell in Home Cage controls ($p < 0.05$). Temperature showed a similar pattern, although with more inter-individual variability. Neither sores nor lesions were noted and changes in physical appearance of the birds during and after deprivation were minor compared to those seen in rats. No birds died and only one deprived bird showed evidence of impaired mobility.
Conclusion: The pigeons seem to show a pattern of changes similar to that seen in rats: rebound including preferential REM rebound, increased energy expenditure, and an increase in body temperature. The failure to see obvious differnces between Deprived and Control animals may be due to technical limitations of the DOW. Pigeons were more successful than rats at letting the disk slide beneath them while they slept, allowing them to get enough sleep (see above) to prevent them from developing the full sleep-deprivation syndrome. As a consequence, stimulation rates were high, depriving the Control birds of sleep. Alternatively, birds may be less vulnerable to sleep deprivation and/or the methods used to pro-

duce it in comparison to rats. It will be important to refine the technique and extend the deprivation period in birds to see if they will ultimately develop the full syndrome._

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Inhibition of NF-κB Nuclear Translocation in Basal Forebrain Reduces EEG Delta Power During Recovery Sleep

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Introduction: Previous studies from our lab have shown that sleep deprivation increased extracellular adenosine in the cholinergic zone of the basal forebrain. 6 h of sleep deprivation also increased A1 receptor mRNA expression and NF-κB DNA binding activity. We also have shown through a series of immunohistochemical studies that sleep deprivation induced translocation of NF-κB into the nucleus and this event is mainly mediated by A1 receptors. Blocking the nuclear translocation of NF-κB, prevented sleep deprivation induced increase in A1 receptor mRNA. In order to examine whether the somnogenic effects of adenosine are mediated via the activation of NF-κB and subsequent expression of genes, we blocked the nuclear translocation of NF-κB using an inhibitor peptide, SN50 (IP).
Methods: Adult male Sprague-Dawley rats were stereotaxically implanted with chronic indwelling EOG, EEG and EMG electrodes for behavioral state recording and bilateral guide cannulae 2mm above the cholinergic zone of the basal forebrain for microinjection. After recovery from the surgical trauma, the rats were acclimatized with the recording cables at least for 2 days. On experimental day 1, continuous baseline recording for 9 h was carried out from 8 am-5pm. On day 2 behavioral state recordings were carried out during 6 h of sleep deprivation (8am-2pm) followed by 3h of recovery sleep (2pm-5pm). On day 3 the rats were bilaterally microinjected with 0.5 µl of 30 µM IP or control peptide, SN50M (CP) and sleep deprivation repeated for 6 h followed by 3 h of recovery sleep, during the same circadian time. To ensure the effect seen during recovery sleep was indeed specific to the sleep following sleep deprivation, we also microinjected on day 4 and 5 with IP and CP followed by 9 h of undisturbed recording. The drugs and procedures were counterbalanced to avoid any bias.
Results: The delta power computed for 3 h of recovery sleep (2pm-5pm) showed a marked decrease (-37%) in IP injected rats when compared to CP injected controls. This coincided with a decrease in NREM sleep (79% for IP v/s 83% for CP, and 84% in control) and REM sleep (4% for IP v/s 7% of CP, and 6% in control). There was no marked difference either in behavioral state or in delta power in rats that received the drugs followed by undisturbed recording.
Conclusion: These preliminary results suggest that blocking the nuclear translocation of NF-κB by IP injection and hence the consequential gene expression (including A1 receptor message) reduces not only slow wave sleep after 6 h of sleep deprivation but also the quality of sleep itself as shown by decrease in delta power. This effect is not because of any non-specific effect of the drug itself. Further, this result is in agreement with a previous report that anti-sense knock-down of the A1 receptor increased waking and decreased delta power during recovery sleep following sleep deprivation.

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The Impact Of Additional Sleep On Test Scores At U.S. Navy Boot Camp

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Introduction: Colleges and high schools have been starting classes earlier than in past generations for numerous reasons, among them providing an earlier start for extracurricular activities. The cost of this trend is that it forces students to get up earlier, thereby reducing the total number of hours in bed. Educational institutions within the military are no exception. For decades at Recruit Training Command (RTC), the boot camp for the Navy, lights out occurred at 10:00pm while reveille sounded at 5:30am. Recent historical trends not only reduced the amount of sleep but also shifted the timing of the sleep so that Recruits awoke much earlier. By early 2002, Recruits were allowed only 6 hours of sleep, from 10:00pm to 4:00am. However, after briefings by Navy sleep researchers to leaders of RTC on the sleep needs of young people joining the Navy, RTC extended sleep for a reveille at 6:00am, effectively delaying the start time of daily exercises and courses by two full hours. Recruits were now allotted 8 hours for sleep time, which continues to the present day. This study is part of a larger effort to determine how Recruits are affected by this two hour extension of sleep.
Methods: We conducted a retrospective analysis contrasting test scores during 2000 and 2001 when Recruits received 6 hours of sleep with test scores for 2003, when Recruits received 8 hours of sleep. We controlled for Recruit ASVAB scores (standardized entry test) to account for differences in scholastic aptitude.
Results: Test scores of Recruits receiving 8 hours of sleep were significantly higher than the scores of Recruits receiving 6 hours of sleep ($p < .001$). There were no significant differences in ASVAB scores across all three years.
Conclusion: This is the first retrospective analysis examining changes in performance that occurred with increased sleep time at Recruit Training Command, Great Lakes. Results indicate that Recruits are performing at a higher level with eight versus six hours of sleep. Based on ASVAB scores, we detected no differences in scholastic aptitude in recruits during the same period. Literature indicates that young people who typify the new Naval recruit (ages 18-20) require 9 hours of sleep, we conclude that this performance gain is based on the two hour extension of sleep time at RTC.

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Animal Model for Shiftwork Resulting in Chronic Partial Sleep Loss

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Introduction: Humans routinely disrupt the normal synchronization of the sleep-wake and light-dark cycles often resulting in chronic partial sleep loss. Only recently have studies examined the impact of chronic partial sleep loss in humans and animal models for chronic partial sleep loss currently do not exist. The objective of this study was to develop an animal model of chronic sleep loss as experienced by shiftworkers who often experience chronic partial sleep loss due to circadian misalignment. To simulate shiftwork, we imposed 12 hours of activity [work] at different circadian times on sleep and circadian rhythms in mice.
Methods: Young adult male C57BL6/J mice (N=20) were entrained to a 12:12 light:dark (LD) cycle and sleep deprived in an enclosed slow rotating wheel [1 rpm] for either 12 hours during the dark phase (N=10) or

during the light phase (N=10) for a period of 10 consecutive days. Core body temperature (cBT) and sleep were recorded prior to (baseline) and during the imposed wakefulness protocol; followed by 14 days of recovery recording.
Results: The onset cBT rhythm of mice did not shift when forced to be active during the light or dark phase compared to controls. Preliminary analysis of sleep data from mice forced to be active during the 12 hour light phase [normal rest phase] and animals in the dark phase [normal active phase] indicate a significant increase in wakefulness across the 24 hour day compared to baseline and recovery periods. During periods of forced activity, mice never obtained REM sleep, but were able to get between 20-50% of baseline levels of NREM sleep. REM sleep increased approximately 4-5% from baseline levels during the 12 hour dark period upon release from forced activity during the 12 hour light phase. Animals did not recover sleep loss during the dark phase, resulting in approximately 26 hours of sleep loss across the 10 day protocol. Mice forced to be active during the 12 hour dark phase did not show significant differences in wake, NREM and REM compared to baseline levels, but did accumulate approximately 26.7 hours of sleep loss across the 10 day protocol. During the recovery period sleep returned to baseline levels on the first recovery day following the 10 days of the protocol for both experimental groups.
Conclusion: Animals do not recover all of the sleep lost each day during the forced activity protocol, resulting in moderate levels of chronic partial sleep loss. The degree of sleep loss is approximately equivalent to a human obtaining 6 hours of sleep per night, which is commonly seen in a shiftwork setting. There are differential effects on both the amount of sleep lost and recovered each day depending on the timing of the period of imposed wakefulness [light or dark phase]. These studies are the first to systematically partially sleep deprive mice for an extended period. An exciting aspect of the data is that results appear to be similar to those seen in data recently published on human subjects exposed to chronic partial sleep loss.

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Performance on an Active Avoidance Task during a Sleep Loss and Circadian Disruption

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Introduction: A common problem for shift workers or anyone attempting to work at night is chronic partial sleep deprivation. Sleep deprivation has been shown to elicit deficits in motor and cognitive performance. The present study attempts to create an animal model for the effects of chronic partial sleep deprivation on cognitive performance.
Methods: Twenty 4-month-old, male, C57BL/6 mice were entrained to a 12:12 light-dark cycle. Animals were placed in a slowly rotating wheel [1rpm] for 12 hours during the light phase for ten days. They were tested at the beginning of their light phase after 12 hours of recovery from the sleep deprivation and given 40 trials per day, for five days in a row to test learning differences. Testing resumed on day ten to measure for differences in memory. The Gemini Avoidance system was used to test learning and memory using speed of crossing and number of crossings as variables. The avoidance system is a two chamber box divided by an open gate, each chamber equipped with a light used as the conditioning stimulus. The active avoidance task was a 60(s) acclimation period followed by a 5(s) light pulse (CS) relative to the chamber the animal was in. If the animal did not move into the non-illuminated chamber they received a 5(s) foot shock (.4mA). The animals received a score of either having avoided the shock, escaped the stimulus, or did not respond to the stimulus. The inter-trial interval was 20 seconds.
Results: The average total accumulated sleep loss was 26 hours over the ten day chronic sleep restriction (see Woods, et al. for details). A repeated measures ANOVA was used to test statistical significance for the two groups. Statistical significance was found for speed of crossing [$F(5,65)63.765$, $p<.01$] and number of crossings [$F(23,299)31.7566$, $p<.01$] between testing days. However there was no significant difference between the chronically sleep deprived group and controls [$F(5,65).78348$, $p=.56529$].
Conclusion: Our data indicates that animals in both groups were able to learn the active avoidance task. However, we found that there is no difference between the chronically sleep deprived animals and control groups, in relation to the variables analyzed. The chronic sleep deprivation protocol did not seem to have an effect on the cognitive performance of the mice despite the sleep loss (26hrs) over the ten days. Our data parallels recent human research such that the mice were able to cope with the loss of sleep (approximately equivalent to humans sleeping 6 hours per night). Future planned studies using this protocol will look at the effects of testing time and strain differences. Additional studies might use a longer sleep deprivation protocol (18 hrs vs. 12 hrs) to better compliment the effects of sleep deprivation on cognitive performance.

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Sleep Deprivation Increases SOD Activity in Basal Forebrain, Brainstem and Hippocampus

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Introduction: We propose that free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS) accumulate during prolonged waking and give rise to the physiological and pharmacological changes associated with sleep deprivation. The accumulation of free radicals such as superoxide (O2.-) and nitric oxide (NO.), depends on the rate of their production and the rate of their removal. Superoxide dismutase (SOD) is the major antioxidative enzyme involved in scavenging superoxide anions. We previously reported that 5-11 days of total sleep deprivation by the disk-over-water technique decreased SOD activity significantly in the brainstem and hippocampus. Here we report that 6 hours of total sleep deprivation significantly increases SOD activity in the basal forebrain, brainstem and hippocampus.
Methods: Male Sprague Dawley rats (400-500 g) were subjected to 6 hours of total sleep deprivation. The rats were placed in individual cages in light:dark conditions (lights on at 8:00 AM and off at 8:00PM) and given food and water ad libitum. The rats were handled daily and novel objects were placed in their cages to get them used to the experimenter and the objects. On the day of the experiment, the deprived animal was kept awake by placing familiar objects in its cage each time it showed physical signs of sleepiness. The control animal was stimulated simultaneously with identical objects. The control animals slept while the deprived animals were spontaneously awake. All animals were sacrificed at 2:00PM by decapitation. Different brain regions were quickly dissected, weighed, frozen on dry ice and stored at -800C. The samples were homogenized in buffer containing 50mM Tris HCl (pH 7.5), 50mM MgCl2 and 5mM EDTA. After centrifugation at 2,000 rpm for 10 mins. at 40C, the supernatant was re-centrifuged at 14,000 rpm for 30 mins. at 40C and this supernatant was used for measuring Cu/Zn-SOD activity. The paired student's t-test was used to determine statistical significance at the level of $p<0.05$.
Results: Six hours of total sleep deprivation significantly increased SOD activity in the basal forebrain by 52% ($t=5.7$, $df=3$, $p=0.01$), in the brainstem by 41% ($t=5.4$, $df=3$, $p=0.01$) and in the hippocampus by 11% ($t=5.6$, $df=3$. $P=0.03$).
Conclusion: Superoxide dismutase (SOD) is the key enzyme involved in the removal of superoxide anions. Increased SOD activity indicates

that sleep deprivation results in the accumulation of free radicals, especially superoxide anions. It is interesting to note that 6 hours of sleep deprivation increased SOD activity, whereas 5-11 days of sleep deprivation decreased SOD activity. We propose that the initial production of free radicals increases SOD activity, and that the continued elevation of free radicals damages the enzyme, leading to decreased SOD activity. Increased free radicals would ultimately lead to oxidative stress, manifested by structural and functional damage to cellular components, thereby accounting for the behavioral and cognitive changes associated with sleep deprivation.

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Sleep Deprivation Effects On Learning And Learning-Induced Neurogenesis

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Introduction: Disruption of sleep disrupts performance on a number of memory tasks, and changes in sleep quality occur after a variety of stimulatory events, underscoring the importance of sleep to memory processes. Recent studies suggest that adult neurogenesis may play a role in learning, specifically in hippocampal-dependent tasks such as spatial learning. As sleep modulates memory consolidation and plasticity it is possible that sleep plays a role in learning-induced neurogenesis as well. This study aimed to determine the effects of sleep-deprivation on learning-induced neurogenesis by using two versions of the Morris water maze task, a spatial, hippocampal-dependent task, and a non-spatial hippocampus-independent task. In a similar study, by Gould et al. (1999), only animals in the spatial learning task had increased neurogenesis.
Methods: 62 Sprague-Dawley female rats were injected twice with 100mg/kg 5-bromo-2-deoxyuridine (BrdU), at ZT02 and ZT10, 7 days prior to the beginning of training. Using the Morris water-maze, animals were trained in one of two conditions: CUE - where the platform was clearly detectable, and changed location every 4 trials; SPATIAL where the platform was submerged, and in a constant location. Training occurred during the last 3 hrs of the dark phase, with 8 trials per day for 4 days. On each training day, at lights onset - half the animals were sleep deprived for 6 hrs (SD). Latency to reach platform was timed, and swim path was videotaped and quantified. Animals were sacrificed, their brains removed, and fixed. 40μM coronal sections of hippocampal slices were processed for combined BrdU and doublecortin (DCX, a selective marker for neurons) labeling. Cell quantification for BrdU-labeled and double-labeled cells was done to assess proliferation\survival, and fate, respectively.
Results: In the CUE learning group sleep deprivation enhanced the rate of learning ($F(1,44)=4.5$, $p=.045$), while for SPATIAL animals, learning was attenuated by sleep deprivation ($F(1,38)=4.01$, $p=.05$). No differences between the SPATIAL and CUE animals in the total number of BrdU labeled cells, and the percent of double labeled neurons were found. Sleep deprivation decreased the total amount of BrdU labeled cells ($\chi2(1)=4.03$, $p=.04$), but increased the amount of cells double labeled with DCX ($\chi2(1)=4.3$, $p=0.04$).
Conclusion: Sleep deprivation had a differential effect on the two types of learning. SPATIAL SD animals performed worse than SPATIAL no-SD animals, while the CUE SD animals fared better than CUE no-SD. Sleep deprivation reduced the number of BrdU labeled cells, which may indicate either suppressed proliferation or reduced survival. However, SD animals had increased number of cells with neuronal fate, an effect that is consistent with the increase in the expression of growth factors in the hippocampus, such as FGF2.

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Effects of Sleep Deprivation on Nitric Oxide Synthase Activity in Rat Brain

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Introduction: Nitric oxide (NO) is produced by three isoforms of NO synthases (NOS): the constitutively expressed endothelial and neuronal NOS (eNOS and nNOS, respectively), and the inducible isoform (iNOS); nNOS and iNOS are cytosolic enzymes, while eNOS is membrane bound. Various brain structures that are implicated in the regulation of the sleep-wake cycle express NOS-immunoreactivity and pharmacological manipulations of NOS elicit a variety of sleep responses. For example, NOS is present in suprachiasmatic nucleus (SCN) neurons and manipulations of the NO system in the SCN elicit phase-shifts and affect sleep in rats, suggesting a role for NO-ergic mechanisms in the circadian regulation of sleep. Our previous studies suggest that NO-ergic mechanisms may also be involved in homeostatic sleep regulation, since injection of a NOS inhibitor decreased both the length and intensity of the sleep rebound following sleep deprivation (SD). To further study the role of NO-ergic mechanisms in homeostatic sleep regulation, the present experiments were undertaken to examine whether NOS activity is affected by SD in various brain structures.
Methods: Male Sprague-Dawley rats were divided into 3 experimental groups: control ($n = 9$), sleep deprived ($n = 9$), and sleep deprived plus recovery ($n = 9$). Rats were kept awake for the first 8 h of the light cycle by gentle handling. At the end of SD, sleep deprived and control (undisturbed sleep) rats were sacrificed, while sleep deprived plus recovery rats were sacrificed after a 24-h recovery period. All brains were quickly excised, sectioned into 1 mm coronal sections and brain regions of interest [SCN, laterodorsal tegmentum (LDT), basal forebrain (BF) and cerebellum (CB)] were dissected by using a 1mm micropuncher. The tissue cores were homogenized, centrifuged and NOS activity was determined by measuring the conversion of [3H] L-arginine to [3H] L-citrulline from both the pellet and supernatant fractions. Total protein content in each sample was determined and NOS activity was expressed as radioactive counts per minute (CPM) per microgram of protein.
Results: There were no differences in NOS activity in the supernatant fraction among brain regions [$F(3,95) = 1.551$, n.s.]. Cytosolic NOS activity was significantly higher than NOS activity in the particulate fraction in all brain regions [47.1 +/- 1.6 vs. 20.9 +/- 1.6 CPM/ug protein; $F(1,204) = 135.9$, $p < 0.05$]. Supernatant NOS activity was significantly different across the experimental groups [control, SD and SD recovery; $F(2,95) = 4.918$, $p < 0.05$]. Following SD, NOS activity was decreased by 18-28% in the supernatant fractions of all brain regions, and returned to baseline levels 24 h later. Particulate NOS activity exhibited significant regional variations [$F(3,93) = 5.235$, $p < 0.05$], with the highest levels observed in the SCN and the lowest in the LDT; however, there were no significant changes in pellet NOS activity in response to SD or subsequent recovery [$F(2,93) = 1.296$, n.s.].
Conclusion: The present findings are in line with the hypothesis that NO-ergic mechanisms may be involved in the homeostatic regulation of sleep.

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The Effect Acute Sleep Deprivation Experienced In A Simulated On-Call Period On Surgical Performance

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Introduction: The ACGME has recently reduced the number of hours that a resident can work per week to 80, and the number in any single on call period to 30. The 30-hour period thus provides mild acute sleep deprivation. While this period is less than what would typically be required for reliable sleep deprivation effects to be observed in an experimental setting, few studies have evaluated its effect on surgical performance. We hypothesized that acute sleep deprivation of the duration regulated by the ACGME would decrease performance on a simulated surgical task.
Methods: Seven surgical residents performed vascular anastomoses on PTFE grafts under sleep-deprived (SD - simulated 30-hour on-call period) and rested (RS) conditions. All residents were employed in full-time research and none were chronically sleep deprived (assessed using sleep diaries and actiwatches). Measures included procedure time, anastomosis size, and anastomotic leak rates quantified by measuring pressure held within the graft at multiple flow rates (1 - 6 liters per minute). Throughout the SD period, PVT, addition and subtraction ability from the Walter Reed Performance Assessment Battery, and occulomotor reactivity testing (FIT), were periodically assessed.
Results: PVT reaction time, addition/subtraction throughput and saccadic velocity all showed circadian effects, but no significant differences between the beginning and end of the 30-hour shift. PVT lapses also did not differ. Procedure times were not different between SD and RS. Anastomosis length was significantly smaller in SD ($p = 0.048$). Pressure held within the grafts was significantly smaller following SD ($p = 0.018$), with the SD - RS differences becoming greater at higher flow rates ($p = 0.007$).
Conclusion: The acute sleep deprivation in these previously well-rested residents did not impact motor speed, cognitive functioning, or occulomotor function. Pressure held by the graft as a measure of anastomotic leak did show a small yet highly significant difference. Data from this pilot study indicate that it is possible for surgical performance to be compromised by the sleep deprivation experienced over a regular 30-hour on-call period, despite no obvious deterioration on more traditional sleep deprivation measures.

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Behavioral Assessment of Attentional Deficits in Sleep Deprived Rats

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Introduction: Although the behavioral effects of sleep loss in humans have been widely studied, little comparable work has been done in animals. The 5-choice serial reaction time test has been shown to be highly senstitive to fluctuations in attention and vigilance in rats. Hence, the attentional performance of rats on a 5-choice serial reaction time task was measured after 4, 7, & 10 h of total sleep deprivation (SD).
Methods: Male Long-Evans rats were food deprived to ~85% of their free-feeding body weight and received food pellets as rewards for performing the operant task. The rats were trained to criteria and subsequently tested in daily sessions of 100 trials at ~16:00 (lights on 08:00 20:00). Sleep deprivation (4, 7, 10h) was produced by gentle handling including sensory and tactile stimulation.
Results: Following 7 and 10 h of SD (09:00-16:00 & 06:00-16:00), the rats exhibited a significant decrease in accuracy, that indicated an impairment of attentional function resulting from the sleep loss. The longer deprivation also produced a significant increase in the number of errors of omission per session relative to control performance, indicating that sleepy rats often did not respond to brief target stimuli. Response latencies also increased significantly in the rats after 7 & 10h SD. Thus, the reduction in performance accuracy cannot be accounted for by the existence of a speed/accuracy tradeoff. After 7 & 10 h of SD the rats also made fewer premature responses, i.e., the error of responding to a port prior to the onset of a light within that port. The reduction of premature responses suggests that the accuracy deficits were due to attentional deficits, and not due to behavioral impulsiveness.
Conclusion: Each of the behavioral effects was generally proportional to the length of sleep deprivation, which suggests that the deficits of selective attention are directly related to the duration of sleep loss. As the relatively short period of SD was able to alter the task performance, longer periods of SD are likely to produce even greater impairment. These data are compatible with human data using the psychomotor vigilance task to assess sleepiness, and indicate the feasibility of measuring attention in sleep deprived rats using this protocol. This test can be used to investigate animal models of sleep disorders, such as sleep apnea, as well as the neurobiological basis of the cognitive impairments associated with acute and chronic sleep loss.

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Feasibility of an Automated Drowsiness Monitoring Device on the Flightdeck

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Introduction: Performance decrements, fatigue and decreased alertness have been identified as a safety concern for flight crews. Consequently, there is a need for an objective approach to detect the presence of drowsiness/fatigue on the flight deck. Results from a scientific validation study conducted by Dinges and colleagues revealed that PERCLOS eye/facial ratings had the highest potential in the detection of drowsiness-induced performance lapses among 6 drowsiness monitoring technologies evaluated. Based on these results, a simulator study was conducted in the cockpit, to establish the feasibility, potential usefulness and applicability of an automated PERCLOS monitor using fixed-based cameras and infrared, retinal reflectance, and automatically generated visual and aural feedback, for drowsiness detection and mitigation on the flight deck.
Methods: In a within-subjects design, N = 24 commercial airline pilots (age 46 ± 10.3 years) flew an uneventful nighttime flight in a high fidelity Boeing 747-400 flight simulator from 0200 to 0800, after having been awake > 18 h, to determine the effects of PERCLOS feedback (in the form of a visual gauge plus an audible alarm and alerts) on: (1) drowsi-

ness (PERCLOS); (2) Psychomotor Vigilance Test (PVT) performance; (3) visual analog scales (VAS) of sleepiness; and (4) physiological variables (EEG, EOG). Participants served as their own controls receiving feedback (treatment condition) and no feedback (control condition) alternating every 75-minutes (in balanced order) during the cruise portion of the flight. This resulted in 4 separate segments of flight, each of which included a pre-PVT VAS measurement and a 10-min PVT test.
Results: A mixed-model regression analysis was performed on PVT lapse data and VAS scores (pre-PVT) within each of the four 75-min segments (at 0316, 0432, 0553, 0708) to compare the feedback to the control conditions. Results showed no significant main effect of feedback on PVT lapsing ($t[60] = 0.97$, $p = 0.33$) and no interaction effect ($F[3,60] = 0.46$, $p = 0.71$), although there was a significant main effect of trial ($F[3,60] = 9.16$, $p < 0.001$). In other words, participants' sleepiness increased across the night. Similar results were found for subjective sleepiness (VAS) scores, with no main effect of feedback ($t[60] = -0.63$, $p = 0.53$), no interaction effect ($F[3,60] = 0.70$, $p = 0.56$), and a significant effect of trial ($F[3,60] = 22.42$, $p < 0.001$).
Conclusion: Preliminary analyses suggested that there was no effect of visual and aural feedback on PVT performance during a simulated nighttime flight in a full-fidelity Boeing 747-400 flight simulator. Additional analyses will be conducted on both the physiological and the online-PERCLOS measures of drowsiness to further determine the effect of real-time PERCLOS feedback administration on alertness and fatigue levels. The results will further address the issue of the feasibility of using a drowsiness monitoring technology, such as automated PERCLOS system, in the cockpit to increase aviation safety.

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Stress Response To Sleep Deprivation Varies With Genotype: Implications For Sleep Regulation

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Introduction: We have previously reported on strain differences in the rebound in EEG delta power immediately following sleep deprivation (SD). AKR/J (AK) mice showed a large increase, C57BL/6J (B6) mice an intermediate increase, and DBA/2J (D2) mice showed no significant increase in delta power. The SD protocol is accompanied by a stress response evident from increases in circulating levels of corticosterone (CORT), a widely used physiological stress marker in rodents. Therefore, strain differences in stress sensitivity and the resulting changes in CORT could affect the delta power rebound in subsequent sleep. To explore this possibility we measured CORT levels after SD and compared them to the levels obtained in undisturbed control mice. CORT levels were also measured in the middle of the dark period to contrast spontaneous periods of wakefulness to the 6-h enforced wakefulness.
Methods: Ten to 13 week old male AK, B6, and D2 mice were used in this study. Mice were divided into three groups. In one group blood samples were taken at ZT6 (Zeitgeber Time 6; i.e., 6 h after light onset; n=9, 11, and 9 for AK, B6, and D2, respectively). In a second group animals were sleep deprived (SD) between ZT0 and 6 by gentle handling (n=8, 10, and 9, respectively) before blood samples were taken. In a third group, blood samples were taken at ZT18; i.e. 6 h after dark onset (n=8, 6, and 6). Plasma CORT levels were measured by radioimmunoassay using a specific CORT antibody (Endocrine Sciences, CA) and [3H] CORT tracer (Sigma, USA). Blood plasma samples (10 microliters) were run in triplicate. Resulting CORT levels were expressed as microgram/deciliter plasma. Levels obtained at ZT6 in the first group were contrasted to the levels obtained in the SD group and the ZT18 group.
Results: In all three strains plasma CORT level were increased after 6-h SD compared to control levels (2-way ANOVA factor 'SD' $P<0.0001$). Control values at ZT6 did not vary among strains ($P>0.67$, t-tests). The relative increase in CORT associated with the SD greatly varied with genotype (2-way ANOVA 'genotype' x 'SD' interaction $P=0.0002$) and was 2.3- to 3.1-fold higher in D2 compared to the two other inbred strains (D2 vs. B6 $P=0.005$; vs. AK $P=0.0006$; t-tests). At ZT18, a time when mice have been predominantly awake for ca. 6-h (75-80% of recording time), CORT levels were significantly increased compared to ZT6 levels in AK mice only ($P<0.02$; t-test). The relative increase after this period of spontaneous wakefulness in AK mice was the same as after the 6-h enforced wakefulness (2.2- and 2.4-fold, respectively). In the remaining two strains, CORT levels at ZT18 did not differ from ZT6 ($P>0.21$) and were significantly lower than in AK ($P<0.02$, t-tests).
Conclusion: The strain differences in stress sensitivity reported here might have contributed to the strain differences in EEG delta power after SD; i.e. the large CORT increase in D2 mice might underlie the lack of an increase in delta power after SD. The relationship between stress and its effect on delta power are, however, not unequivocal; e.g., large increases in delta power have been reported after social stress. Furthermore, the strain differences in the relationship between time-spent-awake and subsequent delta power were also present in undisturbed baseline recordings where prolonged periods of wakefulness are not accompanied by changes in CORT levels in D2 and B6 mice. Nevertheless, the HPA-axis and sleep are intricately interrelated. We will study sleep in adrenalectomized D2 mice with physiological CORT replacement to attempt 'rescuing' the sleep phenotype.

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The Effects of Active Sleep Deprivation on the Developing Brain

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Introduction: It has been well documented that active sleep (AS) is the dominant state during early development in mammals. Previous studies have investigated the role AS may play in early brain development and suggest that AS deprivation during critical stages of development result in marked behavioral changes and reduced brain mass in adult animals. Rat pups between the ages of postnatal day 7 (p7) to 14 (p14) are in a critical period of development that requires a sustained high level of activity within the central nervous system (CNS). We proposed that AS deprivation during this period with induction of prolonged quiet sleep (QS) would precipitate an abnormal increase in apoptosis in the CNS as well as an overall reduction of brain mass, supporting the hypothesis that AS serves as a protective state for the activity-dependent development that occurs at these ages.
Methods: Six rat pups were injected with 25μg/kg of clonidine twice daily, from ages p5 to p14. Six littermates were injected with a saline vehicle following the same schedule. On day nine, pups were perfused and prepared for histology. The brains were sectioned and prepared for Silver Staining. An additional 12 pups under the same age/treatment schedule were assessed for changes in brain mass. Of those 12, four received a 25μg/kg dose of clonidine and were kept awake at set intervals, four received a 25μg/kg dose of clonidine and were left with the dam, and four received the vehicle control. Brain mass was measured at p14.
Results: Clonidine exposure from p5 to p14 produced a positive Silver Stain in one animal from this group. Areas affected include layer 4 of the

cortex, dorsal lateral thalamus, dorsal hippocampus, amygdala, nucleus accumbins, and caudate nucleus. Mean brain mass was reduced in animals that were AS deprived with Clonidine from p5 to p14 compared to controls (1,639mg and 1,712mg respectively $p< 0.00$). Interestingly, animals that were given Clonidine and kept awake had less of a reduction in brain mass than those animals that received Clonidine without further intervention (1,684mg and 1,639mg respectively $p< 0.00$).

Conclusion: This data, along with similar studies, suggests that AS plays a critical role in the development of the central nervous system. Prior literature has shown that AS deprivation results in decreased brain mass in adults, and that certain drugs result in increased levels of apoptosis if administered during critical periods of development. This study demonstrates a specific mechanism for decreased brain mass resulting from AS deprivation, and that brief exposures are sufficient to significantly affect the developing brain. In addition, waking the animal after Clonidine exposure does not result in the level of reduced brain mass as Clonidine given independently, suggesting that it is AS deprivation that precipitates reduced brain mass, and not an unknown effect of Clonidine (effects independent of PS deprivation). Taken together, this data suggests that a possible function of AS is to maintain the high level of CNS activity that is necessary during this critical period of development.

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Relationship Between Modafinil and Cerebral Activation during Total Sleep Deprivation

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Introduction: We previously reported that the brain can compensate for 36 hours total sleep deprivation (TSD) during cognitive performance by recruiting resources not normally used in the well-rested state. In healthy, sleep deprived adults, modafinil has been shown to enhance cognitive performance, particularly during the circadian trough and during attention tasks. The performance effects of modafinil may be due to an enhancement of cerebral resource recruitment or an elimination of the need for such recruitment, but no studies have examined this. We investigated this question by using functional magnetic resonance imaging (FMRI) to compare cerebral responses to cognitive challenges after TSD with placebo or modafinil.

Methods: 15 subjects (age=26.7 ±7.0 years, 7F) were studied with FMRI twice in a counterbalanced order: after 36 hours TSD with placebo and after 36 hours TSD with 200mg modafinil. Medications were given 4 hours prior to scheduled start of the FMRI scans. During each scan, subjects took the psychomotor vigilance task (PVT) and a verbal learning (VL) test. This report compares the active drug and placebo nights with respect to both cognitive performance and FMRI measures of brain activation. We also examined whether modafinil concentrations in the blood on the active drug night affected these outcome measures.

Results: Behaviorally, there were no significant differences between the drug night and the placebo night on any performance measure. For the FMRI data, there were only minor differences between the two nights, but none were observed in task-relevant brain regions. However, there was a significant relationship between modafinil blood concentrations and cerebral responses to the tasks. For the PVT, greater levels of modafinil were associated with increased brain responses in several left prefrontal regions, 1 right prefrontal region, left inferior and superior parietal lobes, and bilateral visual processing regions. No regions showed a negative correlation between drug levels and brain responses. For VL, the bilateral parietal lobes and left posterior temporal cortex showed greater responses with greater drug levels. However, unlike with the PVT, several prefrontal regions showed decreased activation with greater drug levels during VL.

Conclusion: These data suggest the effects of modafinil on cerebral activation during 36 hours TSD may depend on blood concentration levels. For the PVT, increasing drug levels may have promoted cerebral resource recruitment in cortical areas, while not affecting the thalamic and striatal areas we have previously reported as important for optimal reaction times. On VL, greater drug levels may have made additional resource recruitment unnecessary in prefrontal regions, but enhanced recruitment in parietal regions that we have previously reported as involved in cerebral compensation. Alternatively, the inconsistent findings may result from testing subjects too long after drug administration (i.e., after the window of peak plasma concentration). Modafinil has a steep decline in plasma concentration starting at about 4 hours post administration. FMRI sessions typically commenced 4-hours post administration and lasted 1 hour, suggesting some of the effects of the drug may have been diminished during testing. Nonetheless, the apparent dose-response effects observed suggest modafinil may have complex effects on cerebral activation.

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Effect of Modafinil During the Night Shift and on the Commute Home in Patients With Excessive Sleepiness Associated With Chronic Shift Work Sleep Disorder

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Introduction: Shift work sleep disorder (SWSD) is characterized by excessive sleepiness during nighttime work hours and/or insomnia during daytime sleep periods that may impair performance and increase the risk of accidents. The combination of circadian misalignment and cumulative sleep loss can lead to moderate to severe excessive sleepiness, including unintentional sleep episodes at work. This study evaluated the effect of the wake-promoting agent modafinil (PROVIGIL®) on sleepiness and its consequences in these patients during the night shift and on the commute home.

Methods: In this randomized, double-blind, placebo-controlled study, 209 patients with chronic SWSD were enrolled. These patients had objective evidence of excessive sleepiness (mean Multiple Sleep Latency Test [MSLT] score, 2 min) and daytime insomnia (mean polysomnographic sleep efficiency, 74%) at baseline. Patients received modafinil 200 mg or placebo 30 minutes to 60 minutes before each of their night shifts. Subjective levels of sleepiness on night shifts and commute home and difficulty with daytime sleep were assessed by electronic patient diaries completed after working night shifts and after daytime sleep following a night shift. The level of sleepiness on the night shift and commute home were recorded using the Karolinska Sleepiness Scale (KSS). The number of unintentional sleep episodes and mistakes/accidents/near misses during night shifts and commute home were also collected. In addition, patients recorded time in bed and total sleep time for the daytime sleep following night shifts.

Results: One hundred fifty-three patients (73%) completed the study.

Compared with placebo (baseline and postbaseline KSS score [SD]: 7.4 [1.0] and 6.6 [1.3]), treatment with modafinil (baseline and postbaseline KSS score [SD]: 7.3 [0.9] and 5.4 [1.5]) significantly reduced the level of self-reported excessive sleepiness during night shifts (P<0.001 for the change from baseline, modafinil vs placebo). Treatment with modafinil (baseline and postbaseline KSS score [SD]: 5.5 [1.8] and 4.4 [1.6]) also significantly reduced the level of excessive sleepiness on the commute home compared with placebo (baseline and postbaseline KSS score [SD]: 5.9 [1.8] and 5.4 [1.7]) (P=0.01 for the change from baseline, modafinil vs placebo). There were also fewer unintentional sleep episodes (35% versus 44%) and near misses/accidents during the commute home (29% versus 54%; P=0.01) with modafinil-treated patients. Subjective sleep efficiency on days following night shifts was not adversely affected by modafinil. Modafinil was well tolerated in this patient population.
Conclusion: These self-report ratings of sleepiness and its consequences are consistent with objectively measured sleep tendency (MSLT) and performance lapses (Psychomotor Vigilance Task [PVT]). Treatment with modafinil reduces symptoms of excessive sleepiness and its consequences during the night shift and on the commute home in patients with chronic sleep work shift disorder.

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Neonatal REM Sleep Deprivation By Clomipramine Results In Signs Of Ventilatory Pathology

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Introduction: Neonatal suppression of REM sleep by administering clonidine and clomipramine results in adult decreased sexual activity, increased REM sleep propensity and decreased brain weight and DNA concentration 1, 2. Neonatal treatment with clonidine also results in decreased brain level of 5-HT and breathing alterations 3. However, it is not known whether neonatal treatment with clomipramine also produces adult effect on ventilation. Current study will test our hypothesis that neonatal REM sleep suppression by clomipramine would results in a defective development of ventilatory regulation.
Methods: Ten male Long Evans Hooted rat pups were treated with clomipramine (20mg/kg, twice daily, s.c.) and equivolume saline (n=5) from postnatal day (PN) 8 to PN 21. Resting ventilatory behavior, including tidal volume, frequency, and minutes ventilation, were measured using the whole body measurement method when they matured 3. Daily ten-minute measurements were lasted for six days. Statistic were performed using Two factors (treatment X test day) ANOVA. Data measured on the first, the third and the sixth day were processed and presented as mean plus and minus standard error (s.e.).
Results: Comparing with the saline treated control (SAL) rats, rats neonatally treated with CLI (CLI rats) had significantly higher tidal volume in the first test day (CLI=1.03 v.s. SAL= 0.88) but not the third (CLI=0.95 v.s. SAL=0.84) and the sixth day (CLI=0.95 v.s. SAL= 0.84). Two way ANOVA showed that F=5.79, p=0.02 and p<0.05 on the first day test. In addition, CLI rats also had a lower mean frequency than the SAL rats. However, the p value was close to but not less than 0.05 (Two way ANOVA, F=5.19, p=0.052). This implicates that the difference of frequency between groups might be significant if the number of animals in each group was greater. These findings are consistent with the findings from neonatal RSD by Clonidine and suggest that neonatal RSD results in adult pathological ventilation.
Conclusion: Neonatal treatment with REM sleep suppressant, CLI, results in adult breathing alterations. This is consistent with findings from neonatal treatment with clonidine, another REM sleep suppressant with different aminergic effect.

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Sleep Duration Affects The Amount Of Fatigue, Stress, Physical Exhaustion And Mental Exhaustion Reported By Hospital Staff Nurses

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Introduction: Although the role of a hospital staff nurse has always been demanding, todays staff nurses report that their work environments are extremely stressful due to high patient acuity levels, rapid admission and discharge cycles, and an increasingly severe shortage of registered nurses. Nurses no longer work just traditional 8-hour day, evening and night shifts; scheduled shifts may be 12 hours, 16 hours or even longer, and frequently involve overtime. In fact, nurses participating in a recent study reported leaving work at the end of their scheduled shift less than 20% of the times they worked during a 28-day data gathering period. Sleep durations ranged from 0-18 hours, with nurses reporting obtaining on average 6.8 hours of sleep on workdays, and 8.2 hours of sleep on their days off. The goal of this study is to determine if there is a relationship of sleep duration and levels of fatigue, stress, physical and mental exhaustion reported by hospital staff nurses.
Methods: Three hundred and ninety-three randomly selected nurses participated in a larger study of staff nurse fatigue and patient safety. Data collected for 28 consecutive days included information about participants sleep, scheduled and actual work hours, errors, episodes of drowsiness and actual sleep on duty, and difficulties driving home due to sleepiness. In addition, subjects completed daily visual analog scales (VAS) rating their level of fatigue, stress, physical and mental exhaustion. Each VAS consisted of 10 cm horizontal line, with a descriptor at each end of the line, e.g., alert/fatigued, stressed/calm, physically exhausted/energetic, and mentally exhausted/sharp.
Results: Mean VAS scores tended to cluster in the center, with the mean score for fatigue/alertness being 6.8 cm (0=fatigued, 10 = alert). Other mean VAS scores were somewhat lower; 5.71 cm (stressed/calm), 5.44 cm (physically exhausted/energetic), and 5.66 cm (mentally exhausted/sharp). Responses on all four VAS scales were significantly related to sleep duration ($p < 0.0001$). As sleep durations decreased, nurses reported more fatigue and stress, as well as more physical and mental exhaustion. Similar relationships between sleep duration and fatigue, stress, physical and mental exhaustion were observed when work and non-work days were examined separately. Finally, there were significant differences in VAS scores for stress, physical and mental exhaustion on work and non-work days ($p < 0.001$). Participants reported significantly higher levels of stress, physical and mental exhaustion on workdays than non-work days, even when sleep durations was controlled for in the analysis. There were, however, no differences in mean fatigue levels reported on work and non-work days when nurses obtained similar amounts of sleep (p=0.86).
Conclusion: As sleep durations increased, nurses reported being more alert, less stressed, more energetic and mentally sharper. Nurses also reported higher levels of stress, physical and emotional exhaustion on workdays compared to non-workdays.

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The Effect of 24-hour Sleep Deprivation on Startle Responses Associated with Emotion-provoking Pictures

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Introduction: Startle reactions has been shown to be associated with fear conditioning. It was hypothesized to reflect the activation of the withdrawal system of emotion that modulate fear and anxiety. Acute sleep deprivation has been shown to disturb mood in non-depressed individuals and to lead to elevation of mood in some depression patients. However, the effects of sleep deprivation on specifically fear or the withdrawal have not been well studied. The purpose of the present study is to investigate the effects of sleep deprivation on startle blinks in order to enhance the understanding of the mechanisms of sleep and the withdrawal system of emotion.
Methods: Twenty subjects (9 males; 11 females), aged 19 to 23, participated in the study. Their startle blinks reacting to acoustic startle stimulus while viewing emotion-provoking pictures were recorded through vertical electrooculogram. For each subject, measureemnt of startle reactions were conducted twice, once following regular sleep (BL condition) and once following 24-hour sleep deprivation (SD condition), with at least one week in-between the two sessions. Fifty four pictures (18 pleasant, 18 unpleasant, and 18 neutral pictures) were selected from the International Affective Picture System according to the norm. Each picture was present on a computer screen for 6 seconds with an ISI of 6 seconds. Acoustic startle stimulus (100 dB pure tone) were presented randomly while viewing the pictures and during the inter-stimulus intervals.
Results: 2 (conditions) x 3 (pictures) two way ANOVAs were conducted for the comparisons of startle blinks among different conditions. The data showed a significant day main effect for the amplitude measure ($F = 8.85$, $p = .008$) and no significant effects for other comparisons for both amplitude and latency measures. Startle blinks were smaller following sleep deprivation (78.99uV+12.22) than the baseline condition (53.62uV+7.40).
Conclusion: The results indicated that startle blinks were reduced following sleep deprivation. Since the amount of reduction were not different when viewing the pictures of different emotion valences. The reduction of startle reactions may be due to a general decrease of vigilance or arousal levels of the brain that limited the reaction to the startle stimulus.

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Effects of Sleep Restriction on Blood Pressure

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Introduction: The incidence of high blood pressure and heart disease in western society is normally associated with increased life stress and unhealthy eating habits. In addition, prevalence of heart disease continues to rise. We hypothesize that insufficient amount of sleep per night for a prolonged period of time will increase blood pressure even in the absence of changes in diet or weight.
Methods: Forty volunteers, screened by exercise stress tests (standard Bruce Protocol) to rule out any heart conditions, stayed at the Beth Israel Deaconess Medical Center for 16 days as part of a larger study. After 2 baseline nights of 8 hours of sleep per night, subjects were randomised into either an 8-hour (n=18) or a 4-hour (n=22) sleep condition per night for 10 nights. Subjects completed frequent performance batteries and subjective assessments of mood and symptoms throughout the study days. A Clinical Research Center nurse measured blood pressure and heart rate each morning at approximately 7am with a Dinamap blood pressure monitor. Subjects were given a strict research diet, designed to maintain healthy and levels of calories, fat, carbohydrates, protein, potassium and sodium and calculated to maintain admission weight. Uneaten food was measured. On Days 2 and 13 of the protocol, subjects underwent 25 consecutive hours (~10am- 10am) of physiological testing, which included frequent sampling of blood, urine and saliva. Here we report on available blood pressure measures (n=36) taken in the morning of days 1 through 12.
Results: 8-hour control subjects (n=15) showed a pattern of decreasing systolic and diastolic blood pressure without change in heart rate from baseline (morning measures from days 1, 2 and 3) through the 10th day of partial sleep deprivation. Subjects in the 4-hour group (n=21) maintained their blood pressure at the study start levels. The change across days reached statistical significance for diastolic blood pressure (sleep condition by time interaction, $F=2.11$, $p<0.02$), attributable to elevations of approximately 6 dbp after 6 days of insufficient sleep. No change in dietary intake was seen over the course of the study, and there were no significant changes in body weights.
Conclusion: Following un-blinding to their sleep condition in the afternoon of the 3rd day in the protocol, subjects in the 8-hour sleep condition began to habituate to the hospital environment and intensive testing, and blood pressure decreased consistently across days. Subjects in the 4-hour condition maintained a higher level of blood pressure, reflecting elevated physiological stress. Total sleep deprivation has been shown to lead to increased blood pressure. These data suggest that partial sleep deprivation may also be associated with elevated blood pressure.

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Performance and Estimate Performance on a Process Control Task During a Simulated First Night Shift

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Introduction: In recent years, many sleep deprivation studies have focused on very simple vigilance and reaction time tasks as the primary dependent measures. Unfortunately, workers are exposed to work conditions that often demand a wide range of responses. The current study used a task that was designed to closely imitate process control procedures that would occur in a chemical processing plant. The purpose of the current study was to examine performance and estimated performance on a process control task under sleep deprivation conditions.
Methods: The participants were 24 college students who were paid to remain awake for a total of 28 hours. During the last 18 hours of the sleep-deprivation period, the participants were brought into the laboratory and repeatedly completed a number of tasks. One of the tasks that they completed was the Process Control task. This task required the participants to actively monitor and control a simulated chemical plant. To do this, the participants had to monitor gauges that provided information on the system's temperature, fluid, and pressure levels and keep those levels as close to optimal levels as possible. A training period on the task was implemented on the day before the night of sleep deprivation to decrease learning effects. The participants completed four testing peri-

ods during the sleep deprivation condition (5:30 - 9:30 pm, 9:45 pm - 1:45 am, 2:30 - 6:30 am, and 6:45 - 10:45 am). In addition, at the conclusion of the task, the participants completed 2 VAS scales that assessed estimated performance. One of the scales asked the participants to rate how well they did on the task and the other asked them how well they performed on the task.
Results: Performance on the Process Control task was assessed by calculating the average deviation (root mean square error) from the established optimal level for temperature, fluid, and pressure for each participant. There was a significant difference on performance of the Process Control task across the night ($p<.05$). In spite of the prior training on the task, the participants improved their performance from the 1st to the 2nd testing period but then performed progressively worse at the task in the 3rd and 4th testing periods. There was also a significant difference across the night in how the participants assessed their ability to perform. When asked how well they did, the participants estimated their performance as remaining about the same from the 1st to the 2nd testing session but then decreasing throughout the remainder of the night ($p<.05$). When asked how well they performed, there was no significant difference across the night. However, the basic trend was the same between the two VAS scales with no change in estimated performance from the 1st to the 2nd testing period and with decreases across the 3rd and 4th testing periods.
Conclusion: The current study indicates that after an initial learning effect, the participants performed worse on a task that imitates an industrial setting during one night of sleep deprivation. Furthermore, participants did not realize that they experienced a clear learning effect, but did realize that their performance decreased during the last half of the night of sleep deprivation. This result could have implications in industrial settings where workers must assess their own performance when making decisions on whether to continue to work.

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Sleep Deprivation and Off-Duty Activities in Medical Interns

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Introduction: Compliance with the newly instituted ACGME eighty-hour workweek limitation should provide more time away from the hospital and increased time for sleep. A previous investigation at Norwalk Hospital revealed that medical interns are consistently, chronically sleep deprived, even on non-call nights, despite meeting the eighty-hour duty maximum. We hoped to identify the activities interns perform that preclude adequate sleep time. Also, since July of 2003, new work schedules have been implemented within the ACGME mandated 80-hour duty week that increase off-duty time. The aims of this study were to determine which off-duty activities adversely affect time for sleep and whether an improved intern work schedule would increase sleep time.
Methods: Medical interns (n = 12) at Norwalk Hospital volunteered for this study during their Team Care (general non-ICU medical ward) rotations in the fall of 2003. The call schedule is an eight-day cycle with a long call (over night call in house, 24 hours) alternating with a short call (leave hospital by 10 PM, 15 hours) every fourth day. New this year, post-call interns are expected to leave the hospital by 2 PM and there is a mandatory day off (24 hours) per week. Participants completed a daily log covering sleep-wake activity during a 24 hour period in a call month, including days off. A subgroup (n=8) was monitored with actigraphs to confirm logged sleep-wake activity, and completed a detailed life inventory questionnaire which recorded time spent in the following broad activity categories: work time, sleep time, family duties, household chores, exercise, entertainment, academic projects, and career development. Total sleep time (TST) from this year's interns logs and actigraph data was compared with data from last year's interns actigraphs supplemented by log data (n = 9) using 2-tailed t-tests.
Results: Under the new schedule, TST of interns across all nights (call and non-call) was 6.98 +/- 0.5 hours/night (mean +/- SD) compared to 5.27 +/- 0.9 hours/night of TST averaged by interns in last year's 80 hour work week schedule ($p = 0.0003$). Interns showed TST amounts similar to historical controls, 6.74 +/- 1.1 hours/night. The life inventory activity data indicated that TST was less than an optimal 8 hours/night predominantly due to percent time spent for entertainment while off duty. (Sleep 56%, Family Duties/Chores 7.69%, Physical Activity 0.73%, Entertainment 25.5%, Academics 4.75%, Personal Time 5.16%)
Conclusion: In contrast to previous years' interns who worked 80 hours a week, but slept on average 5 and a half hours a night, current interns have average TST of nearly 7 hours a night during a call month. This dramatic increase in regular sleep hours appears to result from scheduled mandatory days off and early work time limits post-call. Although improved, sleep time remains below the average adult need for 8 hours/night. Of all reported off-duty activities, time spent on entertainment may be the greatest barrier to allowing optimal time for sleep in medical interns.

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Mice Display Sex Differences in Wake Time, Sleep Time and Recovery from Sleep Deprivation

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Introduction: Animal models of sex differences in sleep may provide valuable information about the mechanisms responsible for gender influenced sleep disorders in humans. Surprisingly, little information is available on gender differences in sleep in the primary mammalian genetic model for sleep investigation, the mouse. In the current study, we tested whether male and female mice sleep differently from one another and if so, whether gonadal hormones are critical for sex differences in sleep.
Methods: Male and female C57Bl/J6 mice (3-4 months of age) were surgically implanted with electrodes for EEG and EMG recording of sleep and wake states. Animals were maintained on a 14L:10D schedule. Following a 24 hr baseline recording, mice were sleep deprived during the last 6 hrs of the light phase by gentle handling and given a 10 hr recovery opportunity during the following dark phase. In a separate study, male and female C57Bl/J6 mice (3-4 months of age) were gonadectomized and subsequently surgically implanted with electrodes for baseline recording of sleep and wake states in 14L:10D. Control mice received sham gonadectomies. Data were analyzed using ANOVA to detect between (male vs. female) and within (14 hr light vs. 10 hr dark; baseline vs. recovery) factor differences.
Results: ±Over the 24 hr baseline period, female mice spent significantly more time awake (+ 6.91%) compared to males ($p<.000$), at the expense of NREM sleep ($p< .000$). REM remained similar between males and females. The duration of individual wake bouts was dramatically longer in female mice during the dark phase ($p< .01$). In relation, the number of wake bouts in females was decreased in both light and dark phases ($p<.03$). During the 6 hr sleep deprivation period (ZT8-14), males and females lost similar amounts of NREM and REM sleep. The absolute amount of NREM recovery tended to be higher in females than males, but did not reach significance. Because males and females started with different levels of baseline sleep between ZT14-ZT24, it was

important to characterize recovery sleep as a percentage change from baseline. In the 10 hr recovery period (ZT14-ZT24), females had a significantly greater percent change in NREM sleep (+265.89 ± 24.65%) compared to males (+160.3 ± 23.38%) ($p< 0.01$). Recovery sleep for REM was similar between genders in both absolute and percent changes from baseline. Gonadectomies of either male or female mice were sufficient to eliminate the sex difference in both total wake time and NREM sleep over 24 hrs of baseline recording. Castrated males displayed a trend toward increased wakefulness at the expense of NREM sleep while ovariectomized females displayed a trend toward decreased wakefulness and increased NREM sleep. Though neither effect reached significance within gender, each was sufficient to eliminate the difference in wakefulness and NREM sleep between male and female mice ($p>.05$).

Conclusion: The results from this study demonstrate that mice display a sex difference in total wake time and NREM sleep time and that the difference is generated at least in part, by gonadal hormones in male and female mice.

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Preliminary Evidence of an Association Between Work and Sleep Hours on Pediatric Residents' Self- Reported Mood, Attention, and Fatigue

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Introduction: The Institute of Medicine estimates that medical errors cause 44,000 to 98,000 deaths per year in the U.S. It is likely that sleep deprivation may account for at least a small percentage of these errors. The adverse effects of sleep deprivation have been shown to cause at least short-term deficits in neurocognitive and psychological functioning as well as accounting for significant increases in work place and highway accident rates. The current schedules of medical residents leads to a misalignment of circadian phase, acute total sleep deprivation, chronic sleep disruption, and a chronically high sleep debt. We investigated the association between pediatric resident call and work schedules on their self-reported mood and attention fatigue. This was the first part of an ongoing 3-center study of the effects of the ACGME duty hour standards on patient safety, resident safety, and resident education.

Methods: Subjects were 22 medical residents from a children's hospital in a large US city (14 females and 8 males, age 26-33 years). They completed questionnaires each morning for 25 days that included items assessing daily sleep and work hours, subjective ratings of mood and attention as well as other topics not reported here. They marked their response on four visual analog scales, with the anchors sad—happy, tired—rested, calm—tense, and inattentive—focused. These are the dependent variables on which we focus in this report.

Results: Residents' mean total sleep time for the total period was 7.02 hours, and their mean work hours per day was 8.42 hours. They slept for an average of 7.52 hours when not on-call, and 4.32 hours when they were on call. Average sleep following overnight calls was 8.33 hours. Subjects worked for an average of 5.24 hours when not on-call, and 23.70 hours when on-call. On the rested/tired scale, residents' ratings were 5.3 when not on-call, and dropped to 3.1 when on-call, $t(38)=4.14$, $p<.001$. Residents were also happier (5.8) when not on-call and more depressed (4.5) when on-call, $t(38)=2.35$, $p=.02$; more focused (5.5) when not on-call and more inattentive (3.1) when on-call $t(38)=2.74$, $p<.01$; and more relaxed (3.0) when not on-call and more tense (4.4) when on-call, $t(38)=-3.45$, $p=.001$. There was a significant correlation between hours worked and ratings of tension, depression, fatigue and inattention, ($r(40)=.49$, $p=.001$, $r(40)=-.41$, $p<.01$, $r(40)=-.55$, $p<.001$, $r(40)=-.41$, $p<.01$. Interestingly, changes in sleep were not associated with these variables.

Conclusion: When residents are on-call, they sleep significantly less than they do under normal circumstances, and work for extensive hours. We found that the stress of being on-call significantly effects residents' mood, fatigue, attention, and tension. While we found that sleep deprivation does not have a significant impact, our data suggest that consequences of long work hours are decreased attention, impaired mood, and increased tension and fatigue. Extensive wakefulness seems to be a more significant factor on residents' functioning while working than loss of sleep.

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Clinical Significance of Daytime Plasma Orexin-A-like Immunoreactivity Concentrations in Patients with Obstructive Sleep Apnea Hypopnea Syndrome

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Introduction: Polysomnography (PSG) test is very complicated and time consuming, despite its clinical benefits for the diagnosis of patients with obstructive sleep apnea hypopnea syndrome (OSAHS). It will therefore be convenient if a plasma marker is available to choose reasonably the patients who visit firstly the sleep disordered breathing outpatient clinic for the further PSG study. We have recently reported that orexin-A concentrations in plasma collected immediately after waking early in the morning were significantly lower in patients with OSAHS than in control subjects. Accordingly, we conducted the present study to assess the clinical significance of the measurement of orexin-A concentrations in plasma obtained in the daytime as a diagnostic predictor to screen patients with OSAHS.
Methods: The subjects consisted of 19 male patients who visited the sleep-disordered breathing outpatient clinic of the Third Department of Internal Medicine, Iwate Medical University School of Medicine with chief complaints of snoring and/or fatigue in daytime and with the suspicion for sleep apnea syndrome. These 19 subjects had no history of oral administration of hypnotic drugs, and did not have any apparent histories of endocrine, lung, renal or neurological diseases, including narcolepsy, or other diseases such as insomniacs and chronic fatigue syndrome. Blood samples were collected in the daytime from 19 male patients with suspected sleep disordered breathing. Plasma orexin-A concentrations were measured by radioimmunoassay before performing PSG. PSG was conducted in all 19 subjects.
Results: PSG showed that 14 subjects had OSAHS and 5 subjects did not. The daytime plasma orexin-A concentration of the OSAHS patients were 4.9 /-0.8 fmol/mL (mean /-SE), which were significantly lower than those of the control subjects (12.3 /-1.9 fmol/mL) ($p = 0.0004$). Plasma orexin-A-LI levels were less than 7 pmol/mL in 11 out of 14 patients with OSAHS, whereas the levels were above 7 fmol/mL in all 5 non-OSAHS controls. There were significant correlations between daytime plasma orexin-A concentrations and AHI ($r=-0.530$, $p<0.05$), arousal index ($r=-0.476$, $p<0.05$) or ESS ($r=-0.558$, $p<0.05$) in 19 subjects . On the other hand, there were no significant correlations between daytime plasma orexin-A-LI concentrations and AHI ($r=-0.204$, $p>0.5$), arousal index ($r=-0.192$, $p>0.6$) or ESS ($r=-0.082$, $p>0.5$) in 14 patients with OSAHS, probably due to the small number of the subjects.
Conclusion: These findings suggest that the orexin-A concentration in plasma obtained even in the daytime may be a useful plasma marker for screening of OSAHS.

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Cost-Utility Analysis of Three Approaches to the Diagnosis of Obstructive Sleep Apnea (OSAS) and Continuous Positive Airway Pressure (CPAP) Titration

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Introduction: Treatment of OSAS by CPAP is beneficial and cost-effective, but requires careful medical decision making based on diagnostic testing and titration to an effective CPAP level. The standard approach has been full-night polysomnography (PSG) followed by overnight CPAP titration when OSAS is documented. This strategy has been costly and labor-intensive, and increasing demand has presented scheduling difficulties for sleep laboratories. Alternative techniques such as split-night PSG, unattended home studies, and CPAP autotitration have been suggested as a ways to lower costs and improve access of sleep diagnostic evaluations. We constructed a decision-tree model to compare the cost-utility of three common strategies for the diagnosis of OSAS and CPAP titration: full-night PSG; split-night PSG; and unattended partial home sleep study followed by CPAP autotitration. The model was constructed to replicate, as closely as possible, algorithms used in the real world.
Methods: A hypothetical cohort of persons with characteristic symptoms of OSAS was tested. OSAS was defined as an apnea-hypopnea index (AHI) >10 during PSG or a respiratory disturbance index (RDI) >10 during home sleep studies. Values and plausible ranges for probability, utility, and survival variables were derived from published studies. Costs were estimated using 2003 Medicare reimbursement rates. Quality-adjusted life years (QALYs) over a 5-year time horizon were calculated for each of the three strategies examined using previously published utility values and estimated survival rates. Univariate sensitivity analyses were performed to test the effects of a range of plausible probabilities, test characteristics, costs, utilities, and life expectancies over the 5 year time horizon. Two- and three-variable sensitivity analyses assessed the effect of selected simultaneous conditions. A 100,000 iteration Monte Carlo simulation verified the robustness of the model.
Results: The full-night and split-night PSG pathways provided greater QALYs than the home sleep study/CPAP autotitration pathway (3.54 versus 3.49). Expected costs for full-night PSG ($4251.40) exceeded those for split-night PSG ($3780.60) and home sleep study/CPAP autotitration ($3516.30). The incremental cost-utility for split-night PSG versus home sleep study/CPAP autotitration was $5190 per QALY gained. According to the model, full-night and split-night PSG, but not home sleep study/CPAP autotitration, provided a diagnosis of OSAS or no OSAS for all patients. If all patients with unsuccessful or nondiagnostic home sleep studies were followed-up by PSG, the home sleep study/CPAP autotitration pathway had higher expected costs than the split-night pathway with identical QALYs for both. Univariate and multivariate sensitivity analyses differed little from the base-case findings, supporting the robustness of the model and reliability of the conclusions.
Conclusion: For evaluation of OSAS and CPAP titration, split-night PSG is less costly than full-night PSG, and more effective in providing diagnostic and optimal treatment information than home sleep study/CPAP autotitration at an acceptable cost per QALY gained.

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Control of Upper Airway Muscle Activity During Sleep Onset in Patients with Sleep Apnea Versus Controls

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Introduction: Compared to healthy controls, patients with Obstructive Sleep Apnea (OSA) syndrome have increased upper airway muscle activity during wakefulness, driven by activation of a negative pressure reflex (NPR). This increased activity is felt to represent neuromuscular compensation for a smaller and more collapsible pharyngeal airway. At sleep onset (α-È transition), upper airway muscle activity falls in the

apnea patient leading to upper airway collapse. However, it is not clear from these previous studies whether this fall in muscle activity in the apnea patient is due to normal loss of this NPR driven muscle activity at sleep onset or to a greater effect of sleep per se. By employing nasal CPAP to eliminate NPR driven upper airway muscle activity, we could examine the isolated effect of sleep onset in OSA patients and healthy controls.

Methods: We studied 12 younger (ages 18-25) and 11 middle-aged (45-65) healthy men, along with 9 men with moderate OSA (49±5.7 year, RDI=63±39). We measured genioglossal (GGEMG) and tensor palatini (TPEMG), along with airflow and upper airway resistance during wakefulness and sleep onset. EMG was quantified as a percentage of the peak EMG seen during swallowing to allow between subject and between night comparisons. Individuals were studied both on a control night and on a night during which they slept with nasal CPAP.

Results: During control conditions, there was a clear gradation in peak GGEMG among the 3 groups during wakefulness (46.49±2.8 vs. 30.98±2.6 vs.19.82±2.5, % swallow, OSA vs. old vs younger, all $p < 0.05$). This difference was eliminated by the application of nasal CPAP which led to a greater reduction in GGEMG in the OSA patients. At sleep onset, OSA patients had a greater inital reduction in upper airway muscle activity (breaths 1-2 post transition, OSA vs.controls, $p<0.05$), but then showed greater recruitment (breaths 3-5, $p<0.05$). This recruitment in muscle activity was also eliminated by nasal CPAP. On the CPAP night, the change in muscle activity at sleep onset was not different between the groups. Similar findings were seen for the TPEMG as well.

Conclusion: These data suggest that there is a graded activation of the NPR driven upper airway muscle activity in our three groups (OSA>Older>Younger) during wakefulness. With the application of nasal CPAP, the fall in muscle activity at the α-Ètransition was identical in all three groups, supporting a consistent effect of sleep. The recruitment of upper airway muscle activity in the OSA patients after sleep onset on the control night suggests that the NPR may be at least partially active at this time.

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Can Cricomental Space Measurement Accurately Exclude The Presence Of Sleep Apnea?

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Introduction: Cricomental space greater than 15 mm has been recently shown to reliably identify patients that do not have obstructive sleep apnea: negative predictive value of 100% (AJRCCM 2003;167:1427). In this particular study, however, the presence or absence of obstructive sleep apnea was based on portable monitoring without electroencephalography. Conceivably, in the absence of such electroencephalograph measurements, total sleep time may have been systematically overestimated, and consequently apnea-hypopnea index may have been under-estimated. We set out to determine if a cricomental space greater than 15 mm can accurately exclude the presence of obstructive sleep apnea.

Methods: In 104 consecutive patients referred to the sleep disorders clinic, we measured cricomental space, pharyngeal narrowing (grade I to IV), and the presence or absence of overbite. Obstructive sleep apnea was defined by an apnea-hypopnea index greater than 10 per hour based on overnight sleep studies that included electroencephalography.

Results: 89 patients were eligible for the study. Since overbite could not be reliably determined in edentulous patients, 15 patients were discarded from the analysis. The prevalence of OSA was 92% with an apnea-hyopnea index of 38.7 + 27.6 per hour and BMI of 35.6 + 5.7 kg/m2. There were 68 Caucasians, 18 African Americans, 2 Hispanics and one Pacific Islander. Seventy-two of 89 patients (81%) had a cricomental space less than 15 mm, a pharyngeal grade greater than II, and an overbite. The presence of all three such upper airway characteristics was predictive of OSA: the positive predictive value was 95%. Ten of 89 patients (11%) had a cricomental space greater than 15 mm, but the negative predictive value was zero. Seven of 89 patients (8%) fell in a diagnostic gray zone. A cricomental space greater than 15 mm was observed in 39% (5 of 13) African Americans as opposed to 8% (5 of 63) Caucasians ($p = 0.03$; Chi Square).

Conclusion: In our patient population, a cricomental space greater than 15 mm did not exclude the diagnosis of obstructive sleep apnea. A high prevalence of obstructive sleep apnea in our population, more accurate quantification of apnea-hypopnea index, and race differences may have accounted for some of these findings.

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Gender and Obstructive Sleep Apnea: Role of Anatomy versus Respiratory Control Instability

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Introduction: Obstructive sleep apnea (OSA) is approximately twice as common in men as in women. The mechanisms leading to this difference are currently unclear but could include gender differences in respiratory stability, upper airway anatomy or muscle control. The aim of this study was to compare a measure of respiratory stability (Loop Gain, LG) and a measure of upper airway anatomy (Pharyngeal critical closing pressure, PCRIT) between men and women with OSA.

Methods: 11 men and 11 women (mean ± SEM AHI 43.7 ± 6.1 and 43.8 ± 6.4 events/hr respectively) were studied during stable NREM sleep. LG was determined using a proportional assist ventilator. A LG close to 1 indicates an unstable system whereas a LG close to zero implies stability. PCRIT was measured by progressively dropping the CPAP level for 3-5 breaths until the airway collapsed. A regression between pressure and flow during all flow limited breaths was performed and extrapolation to zero flow yielded PCRIT.

Results: Women had a higher body mass index (BMI 38.0 ± 2.4 and 30.0 ± 1.9 kg/m2 respectively, $p=0.02$) but were similarly aged (46.9 ± 2.9 and 45.1 ± 2.2 years, $p=0.6$) to men. LG was near identical in men and women (0.372 ± 0.02 and 0.368 ± 0.02 respectively, $p=0.9$). PCRIT was also similar between genders (+0.35 ± 0.62 in men and -0.18 ± 0.87 in women, $p=0.6$). 6 men and 6 women were matched for BMI (within 1.5 kg/m2). In this sub-group, women tended to be older than men (48 ± 4.3 and 45.6 ± 3.3 years respectively) and have less severe OSA (AHI 34.7 ± 4.1 versus 41.0 ± 7.2 events/hour), however these differences were not significant. Both LG and PCRIT tended to be lower in these women than in men (LG 0.32 ± 0.02 and 0.38 ± 0.03, $p=0.16$; PCRIT -1.4 ± 0.8 and +0.3 ± 1.1, $p=0.22$ in women and men respectively).

Conclusion: These results suggest that both respiratory stability and upper airway anatomy are similar in men and women with equally severe OSA. The contribution of LG and PCRIT to AHI in equally obese subjects appears similar between genders however this requires further study.

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Prevalence and Predictors of Sleep Apnea in Patients Undergoing Bariatric Surgery

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Introduction: Obstructive sleep apnea (OSA) can lead to significant postoperative complications if unrecognized. The goal of this study is to determine the prevalence and predictors of OSA in patients undergoing bariatric surgery.
Methods: We reviewed charts of 60 patients undergoing bariatric surgery who were referred for screening polysomnography (PSG) between September 2002 and October 2003. The following parameters were recorded: Age, gender, historical complaints of snoring, excessive sleepiness (EDS) and witnessed apneas (WA); prior history of hypertension or cardiovascular disease (CVD); Epworth Sleepiness Scale (ESS); body mass index (BMI), and daytime systolic and diastolic blood pressure (SBP, DBP). The apnea-hypopnea index (AHI), base line oxygen saturation (BaseO2), minimum saturation (MinO2), and % sleep time < 90% saturated (T90%) was determined from overnight polysomnography
Results: The prevalence of OSA defined as AHI>15/hr, was 68.3%. Mean age: 44.1 (9.6) years, BMI: 51.6 (10) kg/m2, ESS: 10 (5.9), SBP: 134 (13.6) mm Hg, DBP: 84 (11) mm Hg, AHI: 37.7 (32.5), BaseO2: 93.6 (3.9), LowO2: 72.9 (14.8), and T90%: 16.6 (23.4) %. Multiple linear regression analysis showed that BMI, SBP, DBP, age or ESS was not predictive of the AHI. Likewise, multiple logistic regression analysis showed that a history of snoring, WA, EDS, CVD or gender was not predictive of the presence of OSA (defined as AHI>15). The frequency distribution of OSA severity, based on quartiles of AHI (0-30, 31-60, 61-90, 91-120) was 30, 15, 9, and 6 patients respectively. There was no significant difference in BMI and ESS between the quartiles.
Conclusion: Moderate to severe OSA is prevalent in patients undergoing bariatric surgery. No clinical predictors of presence of OSA or its severity of OSA could be identified in this population. Because of the high prevalence and potential for serious OSA related postoperative complications, all patients undergoing bariatric surgery should be screened for OSA

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The Ventilatory Response to Arousal from Sleep in Obstructive Sleep Apnea: Effect of Upper Airway Resistance

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Introduction: The ventilatory response to arousal from sleep may be an important determinant of respiratory stability/instability and may play a role in the pathogenesis of obstructive sleep apnea (OSA). The increase in ventilation following arousal from sleep may result from the sudden reversal of the increased upper airway resistance (RUA) and hypercapnia present during sleep, or it may represent a waking reflex unrelated to chemoresponsiveness. We designed this study to determine if the ventilatory response to arousal from sleep is influenced by pre-arousal RUA.
Methods: Inspired minute ventilation (VI), RUA and end tidal CO2 (PETCO2) were measured in 22 OSA patients (Mean ± SEM AHI 48.9 ± 5.9 events/hr) during stable sleep on CPAP sufficient to abolish flow limitation (optimal CPAP, 11.5 ± 0.7 cmH2O) and on a lower level of CPAP with stable flow limitation (sub-optimal CPAP 8.2 ± 0.8 cmH2O). A single observer, blinded to respiratory data and CPAP level, identified brief arousals arising from and returning to stable NREM sleep. The pre-arousal conditions and VI on the first breath after arousal were compared between CPAP levels with Student s t-test. VI was also interpolated at 4s intervals for 60s after arousal and compared between CPAP levels with repeated measures analysis of variance (ANOVA).
Results: 16 subjects had brief arousals at both CPAP levels (mean 5 arousals/subject/CPAP level). During stable sleep, RUA was higher on sub-optimal CPAP than optimal CPAP (19.9 ± 4.9 and 2.8 ± 0.3 cmH2O/l/s respectively, $p<0.01$). However VI (7.8 ± 0.4 and 8.1 ± 0.4 l/min respectively) and PETCO2 (43.6 ± 0.8 and 42.5 ± 1.0 Torr respectively) were unchanged between CPAP levels. On the first breath following arousal, VI was higher on sub-optimal CPAP than optimal CPAP (11.2 ± 0.9 and 9.3 ± 0.6 l/min respectively, $p<0.01$). ANOVA also indicated a significant effect of CPAP level and an interaction effect over time.
Conclusion: These results suggest that the ventilatory response to arousal from sleep is influenced by pre-arousal RUA and is not solely dependant on a neural waking reflex.

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Arousal Index Correlates With Multiple Polysomnographic Measurements In Sleep Apnea Patients

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Introduction: Although arousals are frequently seen in sleep apnea patients, little is known regarding the precise relationship between arousal and other polysomnographic variables. The objective of this study was to investigate the correlations between arousal index and the other polysomnogaphic measurements, including respiratory disturbance indices and sleep architecture, in sleep apnea patients.
Methods: Eighty-six (86) sleep apnea patients aged 55 ± 9.5 (range: 35-78) were included in this study. Of them, 63 were male and 23 were female. The rate of male to female was 2.3. Their mean body mass indices (BMI) were 35 (± 7.7) for male and 37.6 (± 8.7) for female. The range of the respiratory disturbance index (RDI) in total sleep time was 10 to 101.1. All of the patients were free of psychotropic medications two weeks prior to the sleep study. Each patient completed two consecutive overnight sleep studies. The measurements included arousal index (AI), RDI in total sleep time (RDI TST), RDI in non-REM sleep (RDI NREM), RDI in REM sleep (RDI REM), oxygen desaturation (SaO2 < 90%) (O2Des), sleep latency, REM sleep latency, sleep efficiency, stage 1, 2, 3, 4, sleep (S1, 2, 3, 4), slow wave sleep (SWS), REM sleep and wake. SPSS 11.5 for windows was used for statistical analysis. Pearson Correlation was chosen to evaluate the correlations between arousal index and the rest of the polysomnographic measurements. To avoid the first night effect, only the data of second night were analysed.
Results: The results indicate that AI correlated with multiple polysomnographic measurements. The values of correlation coefficient (r) were 0.759 ($p = 0.000$) between AI and RDI TST, 0.769 ($p = 0.000$) between AI and RDI NREM, 0.262 ($p = 0.015$) between AI and RDI REM, 0.363 ($p = 0.001$) between AI and O2Des, 0.394 ($p = 0.000$) between AI and S1, 0.231 ($p = 0.033$) between AI and S2, -0.314 (p =

0.003) between AI and S3, -0.238 (p = 0.027) between AI and S4 and -0.314 (p = 0.003) between AI and SWS.
Conclusion: In this group of sleep apnea patients, arousal index correlated positively with RDI in total sleep time, RDI in non-REM sleep, RDI in REM sleep, oxygen desaturation, stage 1 sleep and stage 2 sleep. It correlated negatively with stage 3, stage 4 and slow wave sleep. Arousal index has a negative effect on widely accepted sleep quality measures in sleep apnea patients.

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Body Fat Percentage And Distribution Determines Sleep Stage-Dependant Respiratory Events

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Introduction: The process of respiratory control and contribution of various muscular structures during sleep, and during REM sleep in particular, is a complex and not fully understood. The upper airway, rib cage and abdominal muscles all variably contribute in preserving adequate ventilation through sleep stages. The muscle efficacy can, amongst other factors, be impaired by the infiltration of fat. The purpose of this study is to identify factors relevant to generating stage-dependant respiratory events. The specific goal was to determine the main difference(s) between two groups of patients: those who have primarily REM-related respiratory events and those whose sleep-disordered breathing (SDB) manifests predominantly during NREM sleep.
Methods: We retrospectively analysed a consecutive group of 250 patients diagnosed with SDB in a tertiary sleep clinic. All patients underwent standard polysomnography and physiological measurements that included Body Mass Index (BMI), arterial blood pressure, neck circumference and body fat percentage. The later was performed using a Tanita body fat analyser, which utilises bioelectric impedance analysis method.
Results: From the initial pool of 250 patients two extreme subgroups were sampled (13 and 8 subjects, respectively), one with patients whose Respiratory Disturbance Index (RDI) was low (<5) and RDI in REM was high (>10), and second where the overall RDI was high (>5) and RDI in REM was low (<10). The groups were compared against the BMI, percentage of body fat, neck circumference and major PSG parameters. The statistical analysis showed that these two subgroups significantly differed (p=0.014) only in their percentage of body fat (40.46% ± 13.35 v. 27.5 ± 3.21), and not in BMI (33.11 ± 6.2 v. 30.9 ± 2.8). There was a gender-biased neck circumference difference, with statistical significance disappearing following the stratification. These two subgroups did not differ significantly when comparing other sleep parameters, including sleep efficiency, percentage of REM sleep, sleep duration and other standard PSG measures. The same level of significance was preserved when respective cut-off RDI/RDI REM was 10/10 (p=0.004) and 10/15 (p=0.03).
Conclusion: While the obesity and large neck determine presence of apnoeas/hypopnoeas, they do not have significant predictive value for stage dependent respiratory events. The most important factor determining this variable is body fat percentage and its distribution. Higher body fat percentage and systemic distribution results in the occurrence of predominantly or exclusively REM-related apnoeas/hypopnoeas. Systemic fat infiltration of respiratory muscles results in further impairment of muscle efficiency that normally takes place during REM sleep. When having in mind predominantly regional distribution of fat in males and systemic distribution of fat in females, it is clear that the later type of distribution results in increased number of REM-related events. The trend analysis shows that this difference becomes less apparent as the BMI increases, such is the case in morbid obesity, while it is most robust in mildly obese patients with mild or moderate sleep-disordered breathing. REM-related respiratory events are associated with high body fat percentage and are largely independent of BMI or neck circumference.

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Comparison of Multiple Sleep Latency Test and Maintenance of Wakefulness Test in Patients With Several Degrees of Obesity and With or Without Obstructive Sleep Apnea Syndrome

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Introduction: Obesity can be a significant risk factor for excessive daytime sleepiness independent of sleep-disordered breathing and age. Obesity which is not associated with sleep apnea can cause by itself sleep disruption, daytime sleepiness and fatigue. The aim of this study was to compare several groups of subjects with different Body Mass Index (BMI) with or without the Obstructive Sleep Apnea Syndrome (OSAS) using Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT).
Methods: The sample consited of 170 women and 117 men, mean age 40.5±13.7 (range 17-84) years old. The diagnostic criteria for OSAS was an Apnea Hypopnea Index (AHI) of 5 or greater. The evaluation consisted in two nights of polysomnographic recording following by five-nap MSLT and five-nap MWT (20-min trial) performed consecutively on the same day. The nap-trials were at approximately 9:30 am, 11:30 am, and 1:30 pm 3:30 pm 5:30 pm. The study groups were: Group-1= BMI < 25 Kg/m2 (n=41); Group-2= BMI 25 < 30 Kg/m2 (n=33); Group-3= BMI 30 < 40 Kg/m2 (n=57); Group-4= BMI 40 < 50 Kg/m2 (n=80); Group-5= BMI ≥ 50 Kg/m2 (n=76).
Results: There were not statistically significant differences in the AHI between the different BMI groups: Group-1) AHI=27.5±23.1; Group-2) AHI=34.4±25.3; Group-3) AHI=36.4±29.0; Group-4) AHI=37.8±32.8; Group-5) AHI=45.2±33.3; F=0.53, p=0.71. Mean MSLT differed between the groups, obese subjects with BMI > 30 were more sleepy than non-obese subjects (BMI < 30) even when OSAS was not present (Group-1= 10.4±5.0; Group-2= 9.1±2.7; Group-3= 6.7±5.1; Group-4= 6.7±4.7; Group-5= 5.6±3.9 minutes). OSAS reduced the mean MSLT significantly in the non-obese groups but not in morbidly obese subjects (BMI > 40) (Group-1= 6.6±4.9; Group-2= 6.2±4.0; Group-3= 6.5±4.8; Group-4= 4.9±3.5; Group-5= 4.3±3.4 minutes), one way ANOVA across the groups for BMI condition, F=4.3, p<0.003, Scheffe multiple comparison test: Group 1 >3, 4, 5; p<0.002. For OSAS condition F=9.1, p<0.003. Mean sleep latency on MWT showed statistically significant differences only between the group with BMI < 25 and those with a BMI ≥ 50 (Group-1= 19.2±1.6; Group-2= 15.9 ±1.9; Group-3= 16.7±5.7; Group-4= 15.4±5.4; Group-5= 11.8±5.9 minutes), one way ANOVA across the groups for BMI condition, F= 2.9, p<0.03, Sheffe test: Group 1 > 5; p<0.007. Interestingly MWT did not show any statistically significant differences on sleep latency between the groups with OSAS condition (Group-1= 16.9±4.9; Group-2= 13.2±8.7; Group-3= 14.1±5.9; Group-4= 12.1±6.3; Group-5= 12.2±6.4 minutes), F=2.3, p=0.13. There was not a correlation between age and mean sleep latency on MWT or MSLT. BMI correlated with both MWT and MSLT (r=-0.30, p<0.0001; r=-0.30, p<0.0001, respectively). AHI correlated with MWT r=-0.35, p< 0.0001 and MSLT r=-0.28, p<0.0001.
Conclusion: According with MSLT obese patients without OSAS are more sleepy that non-obese patients. OSAS has an impact on the level of daytime sleepiness only in non-obese patients. In obese patients, it is possible that a "floor effect" would be present. Therefore, obese subjects are so sleepy that there is no possibility to be sleepier even when OSAS is present. The MWT is a sensitive test to the severity of obesity but not to the OSAS condition.

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Pre-Eclamptic Toxemia Tend To Be Associated With Sleep Disordered Breathing And Endothelial Dysfunction As Determined By The Peripheral Arterial Tone

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Introduction: Pre-eclamptic toxemia (PET) is a complication of pregnancy associated with hypertension, edema and proteinuria. There is evidence that PET is associated with endothelial dysfunction (ED), the inability of the blood vessel endothelial cells to release relaxing factors which cause vasodilatation. Some recent studies suggest that women with PET may suffer from inspiratory flow limitation, a form of obstructive sleep apnea (OSA). OSA is a disorder that can further worsen hypertension and is also associated with ED. We hypothesized that women with PET would demonstrate both sleep disordered breathing and ED, and that a correlation between these two would suggest a potential causative association.
Methods: To date, 12 women with PET and 13 control women with uncomplicated pregnancy matched for gestational age have been studied. They underwent clinical evaluation, a nocturnal sleep study to evaluate the respiratory disturbance index (utilizing the WP100 system, Itamar-Medical, Caesarea, Israel) and non-invasive evaluation of endothelial function using a post ischemic hyperemia technique (Endo-PAT, Itamar-Medical, Caesarea, Israel). Endothelial function was quantitatively determined as the ratio of arterial pulse-wave amplitude after occlusion to the pre-occlusion value, corrected for systemic effects (assessed as the corresponding ratio in the non-occluded arm). A higher ratio (endothelial function index) indicates better endothelial function.
Results: The average age, BMI and gestational age of the women with PET and controls were 31±7 vs 30±7 yrs, 30±5 vs 28±7 kg/m2, and 33±4 vs 31±5 weeks, respectively (NS for all). The average PAT respiratory disturbance index (PRDI) was 18.4±8.4 in the PET group vs 10.8±1.5/h in the controls ($p=0.1$). The average endothelial function index was 1.67±0.39 in the PET group vs 1.93±0.41 in the controls ($p=0.07$). There was a weak negative correlation between PRDI and the endothelial function index indicating a tendency toward an inverse relationship between severity of disordered breathing in sleep and endothelial function ($r=-0.33$).
Conclusion: These results suggest that both sleep disordered breathing and endothelial dysfunction are more likely to occur in women with PET than in women with uncomplicated pregnancies. We believe that the borderline statistical significance results from the low number of participants (this study has been powered for 20 participants in each group). The association between PRDI and endothelial dysfunction suggests that respiratory disturbances may contribute to or perpetuate the functional abnormality of the blood vessels seen in women with PET.

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Substantial Improvement In Obstructive Sleep Apnea Using Two Different Oral Appliances Assessed By The Watch-PAT Ambulatory Device

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Introduction: The first line treatment for obstructive Sleep Apnea (OSA) is currently CPAP, but many patients fail this treatment due to the lack of compliance. Dental prosthetic devices that achieve anterior mandibular positioning (AMP) and are used during sleep have been suggested as alternative treatments. These devices aim at increasing airway caliber and decrease airway resistance by advancing the mandible during sleep. We hereby report the usage of two such devices in OSA patients.
Methods: Twenty patients (4f, 16m) with a diagnosis of OSA (mean RDI = 32±18/h, 6 of them with severe OSA defined as RDI>40/h, all refused CPAP treatment) were studied. Patients were overweight (mean BMI 31.7 ± 5.7 Kg/m2), had wide necks (mean neck circumference 17.1 ± 0.9", and reported daytime somnolence (mean Epworth Sleepiness Score of 13.8±4.2). They were randomized to use either the EMA2 or the Silencer oral appliance. Both oral appliances are laboratory fabricated and allow three major functions: vertical and anterior positioning, and free lateral movement. All underwent a pre- and post treatment ambulatory sleep study, using the Watch-PAT100 device (Itamar-Medical, Caesarea, Israel). This device detects sleep state, oxygen saturation, pulse rate and autonomic activation, and has been shown to be accurate at quantifying sleep disordered breathing. The follow-up treatment efficacy study was performed at least 3 weeks on treatment. Vertical and anterior positioning of the oral appliance was determined using the acoustic reflector Pharyngometer (Hood, Pembrok, US).
Results: Ten patients have been using the EMA2 and ten patients the Silencer device on a nightly basis (reportedly). Age, BMI, Neck circumference and pre-treatment OSA severity were similar between the groups. On treatment mean RDI with the EMA2 decreased from 36±17/h to 11±12/h ($p<0.01$) and minimal oxygen saturation increased from 82±6 to 88±4% ($p<0.01$). In 80% of the patients treatment was considered successful (defined as reduction of RDI by at east 50% or to less than 10/h). With the Silencer, RDI decreased from 30±20/h to 13±13/h ($p<0.01$) and minimal oxygen saturation increased from 81±12 to 88±4% ($p<0.05$). In 80% of the patients treatment was considered successful. In both appliances the unsuccessful treatment was in relatively severe patients.
Conclusion: We conclude that both appliances are beneficial for OSA. Although traditionally oral appliances were considered only for mild-moderate patients, our results suggest they should be also considered in severe cases, in patients non-compliant with CPAP.

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Bariatric Surgery for the Treatment of Obstructive Sleep Apnea

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Introduction: It is important to recognize Obstructive Sleep Apnea (OSA) in patients who are to undergo Bariatric Surgery (BS) because of the high prevalence of OSA in morbidly obese patients. In addition, postoperative morbidity is increased in these patients who have OSA and remain untreated. Weight loss may improve many symptoms of OSA and decrease the Respiratory Disturbance Index (RDI).
Methods: We prospectively colleted data from 2001 on patients evaluated for BS. Patients were referred for polysomnography (PSG) if they had a clinical suspicion of OSA. After the PSG, patients who had OSA were treated with either a fixed pressure CPAP (if the effective pressure was <10 cm H2O) or auto-adjusting CPAP (APAP). We used this protocol to avoid repeating a PSG or make changes in the CPAP pressure due to weight loss after surgery. All patients treated with CPAP were encouraged to be compliant with the device till the follow up PSG which was scheduled approximately one year following the BS. The follow-up PSG was delayed beyond one year if they continued to have weight loss. Follow-up PSG was only performed if the pre-op RDI was >10/hr.

Results: There are 134 patients who have undergone PSG and BS. The mean age was 42 with 94 females and 40 males. The mean BMI was 48 kg/m2 ± 8 The mean RDI was 52/hr ± 43. There were 103 patients with an RDI> 15/hr (32 mild OSA [RDI 5-19], 24 moderate OSA [RDI 20-40], 69 severe OSA [RDI>40]). 82 patients were treated with positive pressure devices (45 with CPAP, 6 with Bi-level, 31 with APAP). The mean ESS score was 12 ± 5. So far 10 patients have completed PSG after surgery. There has been a mean decrease in weight of 80 lbs. The BMI at baseline was 50 ± 7 and decreased to 37 ± 4. The mean RDI decreased from 68 ± 40 to 21 ± 18. Five patients have a RDI < 15/hr and have discontinued the use of CPAP. Seven patients (70%) had a greater than 50% reduction in RDI from the baseline. The mean ESS has decreased from 12 ± 6 to 8 ± 6.
Conclusion: High prevalence of OSA in patients undergoing BS suggests that this group of patients should undergo PSG before surgery. Weight loss following BS results in marked improvement of OSA. A substantial number of patients will be able to discontinue the use of CPAP after surgery.

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The Time with Much Motor Vehicle Accidents Caused by Falling Asleep Was 8:00 A.M. in Untreated Patients with Obstructive Sleep Apneas

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Introduction: We conducted a survey at a sleep disorders clinic in Aichi Prefecture in Japan to examine the relationship between untreated obstructive sleep apnea syndrome (OSAS) and traffic accidents, particularly with regard to the time of motor vehicle accidents caused by falling asleep in patients with untreated OSAS.
Methods: After obtaining patient consent, we made a detailed investigation of falling asleep while driving and motor vehicle accidents caused by falling asleep in 931 patients with driver's licenses (710 men and 221 women; mean 45.8 years of old) who were definitively diagnosed as having OSAS based on clinical symptoms and polysomnography between 1998 and 2003. One hundred thirty-nine patients drove professionally, and the remainders were ordinary drivers. If a patient had more than one accident after falling asleep, the most recent accident was investigated. Severity of OSAS was evaluated based on the apnea-hypopnea index (AHI). The control group was made up of 148 ordinary drivers who were in the same age group and had an AHI of <5 and an Epworth Sleepiness Scale score of <7.
Results: 1) Of the 931 patients with driver's licenses who were diagnosed as having OSAS (AHI >5) with daytime sleepiness, 35.0% had fallen asleep while driving in the previous year. The incidence was particularly high in the patients with an AHI of >60, 51.5% of whom had fallen asleep while driving. Both incidences were significantly higher than the value for the control group (18.9%). 2) Ninety-four patients (10.1%) with OSAS had had accidents after falling asleep while driving in the previous 5 years. This was significantly higher than in the control group, in which 8 patients (5.4%) had had accidents after falling asleep. 3) In 82 of the 94 OSAS patients, the details surrounding the accident were able to be confirmed by family members as well as by the patient themself. Most of the accidents in these patients occurred at 9 a.m. The next most common time was between 3 p.m. and 5 p.m. In contrast, few accidents occurred between late at night and early in the morning.
Conclusion: Among the general population, most motor vehicle accidents caused by falling asleep occur between late at night and early in the morning. The next most common time is in the afternoon after lunch. This makes sense, since these are the times when sleepiness in humans becomes more marked for physiologic reasons. However, in patients with untreated OSAS, most motor vehicle accidents after falling asleep occurred at 8 a.m.

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Endothelial dysfunction in sleep apnea patients assessed by Reactive Hyperemia Peripheral Arterial Tonomtry

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Introduction: Obstructive Sleep Apnea (OSA) is associated with increased cardiovascular morbidity and mortality. Recent studies have shown that OSA patients free from overt cardiovascular disease may have endothelial dysfunction which is a sub-clinical precursor state of artherosclerosis. Endothelial function as evaluated in the brachial, femoral and carotid arteries, correlates with the coronary arteries and is abnormal in patients with high risk for atherosclerosis. The current non-invasive mainstay of endothelial function assessment relies on ultrasound measurements of the brachial artery which requires specific training and is highly operator dependent. This limits its widespread applicability. Recently, changes in the peripheral arterial tone during reactive hyperemia (RH-PAT), detected by a novel plethysmographic device, were shown to be correlated with the flow-mediated vasodilation in the brachial artery and the coronary response to acetylecholine, both valid methods of assessing endothelial dysfunction. In the present study we employed the RH-PAT technique to investigate endothelial functioning in OSA patients.
Methods: Twenty-eight patients with suspected OSA (5f, 23m age: 48.7±10.4 yrs) referred for overnight polysomnography (PSG), participated. Their mean BMI and RDI were 29±4Kg/m2 and 30±18/h respectively, with 13 of the participants having severe OSA (RDI>30/h). Nine patients had cardiovascular morbidity and 19 were free of any major disease. In the morning following the PSG all underwent assessment of their endothelial function using the Endo PAT 2000 (Itamar-Medical, Caesarea, Israel). One PAT finger probe was placed on the index finger of the hand undergoing hyperemia testing (induced by 5 minutes of total blood flow occlusion), and the second PAT probe was placed on the contra-lateral index finger. The RH-PAT hyperemic ratio was defined as the ratio of the average arterial pulse wave amplitude during the 1-minute period beginning 90 seconds after occlusion release, relative to average amplitude during a 3 minute pre-occlusion baseline period. To compensate for systemic changes the ratio was normalized to the corresponding ratio from the non-occluded hand. Analysis was automatically performed using a dedicated algorithm (Itamar Medical LtD, Ceasarea, Israel).
Results: The average morning PAT hyperemia ratio was 1.77±0.42 (range: 1.18-2.84, median 1.81) and it tended to be lower in the 9 patients with cardiovascular morbidity (1.58±0.3 vs. 1.86±0.45 , $p<.06$, two tailed t-test). The PAT hyperemia ratio was significantly inversely correlated (Spearman correlation) with RDI ($r=-0.42$, $p<0.02$) and tended to be inversely correlated with percent time below 90% arterial oxygen saturation ($r=-0.28$, $p<0.13$) and BMI ($r=-0.31$, $p<0.10$).
Conclusion: Our results demonstrate that changes in the peripheral arterial tone during reactive hyperemia as measured by the PAT technology were significantly correlated with the severity of sleep apnea syndrome as indexed by RDI. The post-occlusion RH-PAT response was diminished with increased sleep apnea severity, and sleep apnea patients with cardiovascular disease tended to have lower PAT ratios than patients free of cardiovascular morbidity. These finding are in close agreement with previous studies demonstrating endothelial dysfunction in sleep apnea

measured by the brachial hyperemia test. We conclude that measurements of endothelial function using the Endo-PAT 2000 can add important information regarding cardiovascular risk in OSA patients.

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Snoring and Cardiovascular Disease: 2-5 year follow-up after diagnosis of polysomnographically verified primary snoring disorder

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Introduction: Other studies have suggested an increased incidence of cardiovascular disease (CVD) in snorers, without exclusion of sleep-disordered breathing (SDB) by polysomnography (PSG). Our prior study found no increase in CVD in patients with primary snoring disorder (PSD) at the time of diagnostic confirmation by PSG. This study was designed to determine whether CVD developed in the 2 to 5 years after diagnosis of polysomnographically verified PSD.
Methods: PSD was defined as snoring without daytime sleepiness (Epworth sleepiness score [ESS] < 10, multiple sleep latency test [MSLT] > 10), sleep disruption (arousal index < 10 arousals/hr), or sleep disordered breathing (SDB). The inclusion criteria were: 1) age > 18 years, and 2) PSD. The exclusion criteria were: 1) absent ESS, 2) nocturnal hypoxemia (SaO2 < 88%), 3) hypoventilation (PaCO2 > 45mmHg), 4) periodic limb movement disorder, 5) narcolepsy, 6) upper airway resistance syndrome (UARS), or 7) obstructive sleep apnea (OSA) in any position or sleep stage. Charts of patients having undergone PSG between 1997 and 2001 were reviewed for the diagnosis of PSD and for history of CVD. Those patients with PSD were then contacted via phone to complete a follow-up investigation, concerning development of CVD and other medical conditions over the follow-up period of 2-5 years.
Results: We reviewed 5150 charts, 44 of which met our inclusion and exclusion criteria and were further reviewed for the presence of hypertension (HTN) and coronary artery disease (CAD). Compared to the 1999 US population and the 2001 Houston population, the prevalence of HTN and CAD among the PSD subjects was not statistically significant. Of the 44 subjects initially diagnosed with PSD, we were able to contact 20 patients for the follow-up investigation. The time interval for follow-up ranged from 2 to 5 years. Five percent of the subjects were contacted at 2 years, 60% at 3 years, 25% at 4 years, and 10% at 5 years post PSD diagnosis. The follow-up sample contained 45% females, 55% males, and had a mean age of 37.1 ± 9.47 (SD) years. The mean ESS was 5.55 ± 2.46 at the time of PSD diagnosis and 6.55 ± 3.07 at the time of follow-up (p = 0.263). Fifteen percent of the sample had HTN at the time of PSD diagnosis, which increased to 20% at the time of follow-up. The percent of CAD in this sample remained the same (5%) over the follow-up time period of 2 to 5 years. In comparison to the 2001 Houston population, there was no statistically significant increase in the prevalence of HTN in the PSD subjects (OR 1.4047; 95% CI: 0.4689-4.2082; p = 0.376). In comparison to the 2001 Houston population, the prevalence of CAD in the PSD subjects was not statistically significant (OR 1.6489; 95% CI 0.2197-12.375; p = 0.519). Of the 20 PSD subjects evaluated, only one (5%) developed HTN in the follow-up period, and that was 3 years after initial diagnosis. The one subject who developed HTN also reported an increase in ESS from 1 at the time of PSG to 10 at the time of a 3 year follow-up. No one reported development of CAD in this 2-5 year interval.
Conclusion: When SDB (OSA, UARS) is excluded by PSG, there appears to be no association between snoring and HTN or CAD. Over a 2 to 5 year follow-up, we found that there was no significant increase in HTN or CAD in primary snorers.

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Observations of a Urology Population: Are Nocturia Patients Hiding Obstructive Sleep Apnea Syndrome?

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Introduction: Nocturia is a frequent symptom of obstructive sleep apnea syndrome (OSAS). Previous studies in OSA patients have shown a high prevalence (older age and higher RDI being the strongest predictors). Thus, patients with undiagnosed sleep apnea may present to the urologist with nocturia as the first complaint. If so, improved recognition of the association of nocturia with OSAS would be important. The goal of this study is to assess the prevalence of OSAS symptoms in patients seen for nocturia in a urology practice.
Methods: The study included adult urology patients with nocturia (defined as 2 or more awakenings nightly for urination). Patients completed a self-administered survey (between September and November of 2003) to identify the presence or absence of the following sleep symptoms: snoring, difficulty staying awake during the day, waking-up frequently from sleep, excessive daytime sleepiness (EDS), gaining ≥ 10 pounds in the last year, waking-up with choking sensation, excessive sweating while sleeping, usage of sleeping aids, headache on waking up from sleep, frequency of nocturnal urination, and reported leg jerks and breathing-pauses while sleeping by bed-partner.
Results: The sample included 71 patients, with mean age of 68.2 ± 14.4 years, 62 (87%) men vs. 9 (13%) women. The mean nocturia frequency was 2.9 ± 0.8 urination/night. Symptoms were as follows: snoring 46%, difficulty staying awake during the day 10%, waking-up frequently from sleep 70%, EDS 8%, gaining ≥ 10 pounds in the last year 14%, waking-up with choking sensation 6%, excessive sweating while sleeping 8%, usage of sleeping aids 13%, headache on waking up from sleep 1%, reported leg jerks 10%, and reported breathing-pauses while sleeping 14%. Overall, 33 patients (46%) reported snoring. This group was younger (64.3 ± 15 vs. 71.6 ± 13.3; p=0.03) and had more reported breathing pauses while sleeping (8 vs. 2, 24% vs. 5%; p=0.02) than the no snore group. Twenty-three patients (32%) were categorized as high probability of OSAS (positive responses to snoring, EDS, difficulty waking up, difficulty staying awake, breathing pauses, and / or choking). Six of those had a full polysomnography, and 5 of the 6 (83%) were diagnosed with OSAS (Mean respiratory disturbance index of 40.3 ± 35, range 8 to 80).
Conclusion: OSAS symptoms are frequent in nocturia patients. Those patients with high-risk responses, while a small subset, had a high prevalence of documented OSA. Follow-up of the urology population with comparison of patients with and without nocturia is planned.

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Cognitive Functioning In Patients With Dementia And Sleep Disordered Breathing Is Related To Nocturnal Oxyhemoglobin Saturation Prior To Sleep

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Introduction: Patients with sleep disordered breathing (SDB) often suf-

fer from some cognitive dysfunction. This observed impairment on cognitive testing has been attributed to nighttime intermittent hypoxemia and sleep disturbance. The number of nocturnal desaturations per hour of sleep and the minimal oxyhemoglobin saturation level are used to determine the severity of the disorder. This analysis is part of a larger study evaluating the effect of CPAP on cognitive functioning in patients with dementia and SDB. It is aimed at assessing the relative importance of various polysomnographic measurements in predicting cognitive performance and mood and fatigue changes in patients with dementia and sleep disordered breathing. We hypothesized that parameters relevant to severity of sleep apnea would be associated with cognitive functioning, sleepiness and mood.

Methods: The present analyses are based on pretreatment data from 21 participants in an ongoing randomized, double blind, placebo-controlled trial of CPAP among patients with Alzheimer disease (AD). Participants included 18 men and 3 women with mild-to-moderate physician-diagnosed AD; mean age was 78.9 years (SD=7.69), mean education was 14.9 years (SD=3.1); the majority of patients (90%) were Caucasian ethnicity. The mean BMI was 24.2 (SD=2.3). Each had home polysomnography (Embla, Medcare) to confirm the diagnosis of SDB (defined as an RDI>10). Cognitive tests included: the Mini-Mental State Exam (MMSE), Hopkins Verbal Learning Test - revised, Digit Span, Digit Symbol-Coding, and Symbol Search, 64-card version of the Wisconsin Card Sorting Test (WCST), Stroop task, letter (FAS) and category (Animals) fluency, and Trail Making Test (parts A and B). Patients completed the Pittsburgh Sleep Quality Inventory, Functional Outcome Sleep Questionnaire (FOS-Q), the Cornell Depression Scale (CDS), and the Epworth Sleepiness Scale (ESS). Spearman correlations were calculated between polysomnographic measurement cognitive score, and the other clinical rating scales.

Results: Among the polysomnographic respiratory variables, the strongest correlate of cognitive functioning was wake saturation, e.g., lower wake saturation, as measured prior to sleep, was associated with more WCST perseverative errors ($r=-.51$, $p<0.05$) and perseverative responses ($r= -.49$, $p<0.05$), and with fewer correct words generated on the fluency task ($r=.603$, $p<0.01$). Lower wake oxyhemoglobin saturation was also associated with less vigor on the FOS-Q ($r=.586$, $p<0.01$), and more depression on the CDS ($r=-.50$, $p<0.05$). Interestingly, no significant correlations were found between RDI and the cognitive, functional, or depression scores.

Conclusion: These results show that baseline nocturnal saturation prior to sleep is highly correlated with performance on at least some aspects of cognitive functioning (e.g. executive functioning), as well as subjective rating of vigor and depression. While preliminary and needing replication with a larger sample, these findings suggests that wake nocturnal saturation may be an important predictor of cognitive and other functionally relevant behaviors.

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Fatigue in Sleep Disordered Patients: The Contribution of Gender and Depression

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Introduction: Fatigue is identified as often as excessive daytime sleepiness (EDS) as the chief daytime complaint of apnea patients. Depression, meanwhile, has been shown to contribute to the variance of self-reported fatigue in apnea patients. In addition, both depression and fatigue are more common in women. No study in sleep patients, however, has been powered to detect gender differences as well as assess other mediators of fatigue, while also utilizing validated measures of both EDS and fatigue. Accordingly, we used validated measures in a large clinical sample to test our hypotheses that: fatigue would be as highly prevalent as EDS, that their proportions would not vary across categories of AHI severity, and that both depression and female gender would be significant predictors of fatigue.

Methods: This cross-sectional study used a random sample of 820 adults undergoing standard, diagnostic PSG scored according to R&K criteria (mean quarterly assessed kappa 0.82). Prior to PSG all patients completed the Epworth Sleepiness Scale (ESS), Profile of Mood States (POMS) and Zung Depression Scale (Zung). The study sample consisted of 540 (66%) patients who completed all questionnaires with no missing data; they did not differ from those excluded for missing data on demographic or study variables. Patients were stratified into three AHI categories: <10, 10 to 39, and > 40. Fatigue was analyzed across AHI categories using ANACOVA, controlling for EDS and accounting for depression, age, and gender as covariates. A multiple regression model was built to explain variance in fatigue. All analyses were conducted with SPSS 11, were 2-tailed and set alpha at .05.

Results: In our sample, 57% exceeded the clinical criterion for sleepiness (ESS >10) and 52% reported fatigue one SD above the normative mean for the POMS. Furthermore, our ANOCOVA model for mean fatigue across AHI groups did not reach significance ($F=1.58$, $p=0.21$). In secondary analyses, a cut-off of AHI = 15 for the low AHI group achieved similar results and replacing AHI with either the arousal index or the REM AHI did not alter findings. Fatigue and EDS were only weakly correlated with each other ($r = 0.28$, $p < .001$), which held true for both genders. Depression was significantly correlated with both fatigue and EDS ($r = 0.53$ and 0.24, both $p < .001$), with a stronger relationship existing between depression and fatigue, than depression and EDS. These findings held within AHI categories and across gender. Also, in terms of gender, despite being equally sleepy, but more fatigued than men, women had a lower mean AHI. Finally, our regression model for fatigue, which included depression and EDS as independent variables and also tested age, gender, BMI, AHI, arousals, and all interaction terms, was significant ($F=79.96$; $p<.001$) and accounted for 31% variance in fatigue. As expected, both depression and sleepiness were significant predictors of fatigue. Contrary to our hypothesis, gender did not contribute to fatigue.

Conclusion: Fatigue is highly prevalent in apnea patients, but not related to AHI category or to continuous AHI severity. The modest relationship between fatigue and EDS suggests that while there is overlap between constructs, fatigue is distinct from sleepiness. Therefore, we echo recent calls for fatigue to be attended to in sleep patients. The finding that although women were more fatigued, gender was not a predictor of fatigue was not explained by conventional measures of apnea severity or arousal, or by depression as a third variable. Instead, the strong association of depression with fatigue in both genders and its contribution to fatigue variance, suggests that fatigue which is refractory to standard apnea care may be mediated by depression. Alternatively, it will be interesting to further establish whether standard care for apnea reduces fatigue.

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Apnea Positive Pressure Long-Term Efficacy Study (APPLES): Preliminary Studies

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Introduction: APPLES is an NHLBI-sponsored, blinded, 6-month, sham-controlled, multi-center outcome trial of CPAP therapy. We com-

pleted two preliminary studies at Stanford University.
Methods: Subjects were 16 patients recruited from Stanford Sleep Disorders Clinic; 10 for the first pilot study and six for the second. The combined sample consisted of 14 men (12 Caucasian, 1 Hispanic, 1 Asian) and 2 women (1 Caucasian, 1 African American), with an age range of 28 - 65 years. The inclusion criteria were RDI≥10, age≥18 years, and on stable medications for 2 mos. The exclusion criteria were severe OSAS, prior OSAS treatment, near misses or MVAs due to sleepiness, other clinically significant sleep disorders, or serious/unstable medical conditions. The study was IRB-approved and all subjects gave written informed consent. Baseline studies consisted of an overnight PSG, followed by tests the next day. Testing included a comprehensive battery of neurocognitive measures (the Sustained Attention Metric Working Memory Task [SWMT] developed by Gevins and colleagues that assesses working memory and sustained attention with concurrent recording of EEG, Psychomotor Vigilance Task [PVT], Subcritical Visuomotor Tracking Task, Digit Symbol Substitution Test, Trails Making A and B Tests, Paced Auditory Serial Addition Task, Buschke Verbal Selective Reminding Test, Stroop Color and Word Test); sleepiness assessments (Maintenance of Wakefulness Test [MWT], Epworth and Stanford Sleepiness scales); mood assessments (the Mini International Neuropsychiatric Interview [MINI], Hamilton Depression Rating Scale [HAM-D], Profile of Mood States [POMS], Beck Depression Inventory-II [BDI-II]); and quality-of-life (Calgary Sleep Apnea Quality of Life Index [SAQLI], Quality of Well-Being Scale (QWB-SA]). Repeat testing occurred after one month of active or sham CPAP.
Results: The baseline RDI means (standard deviations) of 28.9 (23.1) for the active group and 30.2 (22.4) for the sham group were not significantly different. The 8 subjects randomized to active CPAP had pressures ranging from 7 to 10 cm H2O during the CPAP titration study, while the 8 subjects randomized to sham CPAP had pressures at 0.3 cm H2O. The two groups were not statistically different in the amounts of their CPAP use (active CPAP group mean of 5.4 hrs vs. sham CPAP group mean of 5.2 hrs). After one-month of CPAP, on average, the active group showed improved alertness on the SWMT, whereas the sham group showed decreased alertness, resulting in an effect size of 1.01 ($p = 0.08$). The effect sizes (in parentheses) for domains of neurocognitive function were: attention and psychomotor function (0.01-1.02), learning and memory (0.26), executive function (0.14-1.32). For the active group, out of the total of 32 post-CPAP MWT trials, there were only 6 trials below the lower normal threshold of 11 minutes, while for the sham group 28 were below this threshold. Similarly, subjects in the active group showed a trend for improvement in Epworth and Stanford Sleepiness Scale scores. In terms of emotional functioning, there were no consistent trends in the results from MINI, HAM-D, BDI-II, or the POMS. Seven of the 8 subjects in the active group (vs. 3 of 8 in the sham group) showed improvement in their SAQLI scores. For the QWB-SA, there was a mean improvement of 0.04 (0.13) for the active group and a mean improvement of 0.01 (0.15) for the sham group.
Conclusion: Our preliminary studies are among the few randomized double-blinded controlled trials for CPAP therapy to use an adequate placebo control group. We found improvements in measures of neurocognitive function, mood, sleepiness, quality of life, and sleep-disordered breathing in subjects effectively treated with CPAP compared to both their baseline levels and to subjects receiving sham CPAP. Although of limited sample size, these results suggest that our assessments, many of which are measures in APPLES, are sensitive to the effects of CPAP.

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Non specific Pacemaker Programming does not affect Sleep or Sleep Disordered Breathing in Pacemaker Patients

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Introduction: Sleep disordered breathing (SDB) adversely affects cardiovascular health in population based clinical trials. Recent preliminary studies have shown potential benefits of atrial overdrive pacing in reducing SDB. We studied the characteristics of sleep and SDB in a cohort of patients with cardiac pacemakers (PM). In addition, we evaluated whether cardiac characteristics or programmed pacing parameters affected sleep quality in these patients.
Methods: Patients with previously implanted PM (Class I or II indications) were screened for SDB risk. High risk patients underwent an overnight sleep study. Pacing mode and lower rate limit (LRL) were left at the investigators' discretion. Total sleep time (TST), sleep efficiency (TST/time in bed), sleep stage (stage 1-2, slow wave and REM sleep), arousal (events/hour), oxyhemoglobin saturation (SaO2), and apnea-hypopnea index (AHI) was analyzed. Multiple regression analysis was used to determine which independent variable, if any, correlated with AHI. Independent variables included patient age, BMI, LVEF, heart rate during sleep (SHR) and PM LRL.
Results: 49 patients out of 78 screened patients were found to be at high risk for SDB, thirty patients (25 Male) participated in the sleep study. PMs were programmed in DDD (n=14), DDDR (n=14), VVI (n=1) or VVIR (n=1). Patients were 65±10 yrs, with BMI of 29±5, LVEF of 53±13%. SHR was 68±10 bpm, while programmed LRL was 60±7 bpm. Sleep and SDB related measurements are presented in the table. Twenty-six (87%) patients had an AHI >= 30. Multivariate analysis did not show significant correlation between patient characteristics and AHI (SHR $p = 0.1$, all others $p > 0.15$). PM LRL did not significantly correlate with AHI ($p > 0.15$).
Conclusion: Sleep studies in these cardiac pacemaker patients demonstrated prevalent and severe sleep apnea syndrome. Neither sleep heart rate nor PM lower rate limit was predictive of AHI in this study. Non-specific pacemaker therapy had no clinical impact on sleep apnea in these patients.

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The Effects of Oral Zolpidem on Nasal Continuous Positive Airway Pressure (CPAP) Compliance in the Treatment of Obstructive Sleep Apnea (OSA)

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Introduction: Nasal continuous positive pressure (nCPAP) is the treatment of choice for most patients with obstructive sleep apnea syndrome (OSAS), but is not always well tolerated. Patients who have a positive initial experience with nCPAP are more likely to accept therapy and remain compliant. Our anecdotal experience suggested that a mild hypnotic medication facilitated sleep onset and improved acceptance of

nCPAP in some patients. We conducted a randomized, double-blinded, placebo-controlled study of a hypnotic medication (zolpidem) in patients newly diagnosed with OSA who were initiating therapy with nCPAP and assessed acceptance of nCPAP and compliance data at 28 days.
Methods: Patients who were newly diagnosed with OSAS (Respiratory Disturbance Index (RDI) >5 and Epworth Sleepiness Scale (ESS) >10) and prescribed nCPAP were consented for entry into the study and randomized to one of three groups: 1) zolpidem 10 mg PO for 14 days, 2) placebo for 14 days, or 3) standard care (no medication). Patients were instructed to take medication 30 min prior to bedtime. Patients completed the ESS and the Functional Outcomes of Sleep Questionnaire (FOSQ) at entry. Compliance data were collected over a 28-day period and patients were reevaluated at day 28 with a repeat FOSQ and ESS. Parameters evaluated included number of days with CPAP use, total number of minutes of CPAP use, patient tolerability and agreement to continued use, and changes in sleepiness score as well as changes in quality of life scores.
Results: 71 male patients (age 22-59) were enrolled and randomized. Groups were matched for age, BMI, ESS and FOSQ. Despite randomization, the standard care group had a higher RDI (52.8 standard care vs. 29.4 zolpidem and 32.1 placebo, p=0.011). Compared to placebo and standard care groups, the zolpidem group did not show greater CPAP usage in terms of total days used (zolpidem 20.8 vs. placebo 19.3 vs. standard care 22.9; p=0.23) or overall minutes used per night (257 min vs. 264 min vs. 287 min; p=0.46). Within the group taking zolpidem, there was no difference in CPAP usage during the period on medication compared to the period off medication (227 min vs. 181 min, p=0.23). Patients randomized to zolpidem did not have increased use compared to placebo or standard care during the 14-day course of medication (227 min vs. 229 vs. 252 min, p=0.73) or in the 14 days after taking the medication (182 min vs. 186 min vs. 225 min, p=0.34). All groups demonstrated statistically significant decreases in both the ESS ($p<0.001$) and the FOSQ ($p<0.001$). The initial RDI was not predictive of the change in ESS (p=0.15) or FOSQ (p=0.31).
Conclusion: Sleepiness scores and quality of life measures improved in all three groups on nCPAP. We were unable to demonstrate improved nCPAP tolerance or compliance with empiric use of a fourteen-day course of zolpidem when initiating nCPAP therapy. The empiric use of a hypnotic agent to improve nCPAP tolerance and increase compliance is not recommended.

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Comparison of Central Sleep Apnea with Randomly-Selected Sample of Obstructive Sleep Apnea
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Introduction: Central Sleep apnea (CSA) is a disorder with varying clinical presentation and recurrent episodes of an absence/diminution of respiratory effort during sleep. The purpose of this study is to compare the demographic, clinical and polysomnographic (PSG) characteristics of CSA relative to a randomly-selected obstructive sleep apnea (OSA) population.
Methods: CSA had a Central AH index > 5/h and OSA index < 5/h. Central apnea/hypopnea was defined as a >80%/>50% decrease in peak oral/nasal flow, accompanied by a proportional decrease in peak thoracic/abdominal respiratory effort. OSA was defined as obstructive AH index > 5/hr and central AH index < 5/hr. We retrospectively reviewed charts and diagnostic PSGs of patients diagnosed with CSA in last 18 months (n = 20) and OSA patients who were randomly selected from our sleep center clinical database (n = 37).
Results: In our clinical data base, the prevalence of CSA was 20/1547 (1.3%) and the prevalence of OSA was 629/1547 (1.3%). Race distribution in CSA patients was 17/3 C/AA, in OSA patients 20/17 C/AA, P= .019. There were no differences in age and gender distribution or BMI (35/36 CSA/OSA P = NS) between the two groups. Patients with CSA presented less often with snoring, (10/20 vs. 28/37 P = .021). There was no difference in Epworth sleepiness scale (ESS) between the two groups. A history of coronary artery disease (CAD) was more prevalent in CSA (8/20 vs 6/37, P = .04) but hypertension was less prevalent in CSA patients (3/20 vs. 16/37 P= .031). In reviewing PSG data there were no significant differences in sleep onset latency, sleep efficiency and sleep stage time between the two groups. However periodic leg movements (PLM) were more prevalent in CSA (27 ± 76 vs. 4.9 ± 12.4, P = .001).
Conclusion: In an obese sleep center referral population CSA without obstructive apnea does exist, albeit in a small population. CSA and a randomly-selected OSA group were similar in age, gender and BMI, differed in race, CAD and PLMs, but less frequently had a history of snoring.

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A Differential Effect Of Intermittent Hypoxia And Sleep Fragmentation On Sleep Architecture In The C57Bl/6J Mouse
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Introduction: Obstructive Sleep Apnea (OSA) is characterized by recurrent collapse of the upper airway during sleep leading to periods of intermittent hypoxia (IH) and sleep fragmentation (SF). Animal models have previously shown that IH leads to a variety of adverse cardiovascular, metabolic, and neurocognitive outcomes, which could result from the effects of hypoxia per se or due to hypoxia-induced SF. However, it remains unknown whether IH disrupts sleep architecture in a pattern that simulates human OSA. Furthermore, it is unclear whether the impact of IH on sleep is more severe than that caused by SF without hypoxia.
Methods: Five male C57BL/6J weighing 27-30 g were instrumented for EEG and EMG recording and acclimated to 12 hrs light/dark cycle. After recovery for 5-7 days, a 24 hr period of baseline polysomnogram (PSG) was recorded. Mice were next exposed to either IH (FIO2 declined from 20.9% to 5.0% over a 30 sec period and reoxygenated to room air levels in the succeeding 30 sec period) or non-hypoxic SF (three immediately successive 30 lpm high flow air blasts of 1, 2, and 3 seconds duration administered at 60 seconds intervals) during the light phase for 5 days. PSG was continuously recorded throughout the exposure and during a subsequent 24 hr recovery period. Animals were allowed to rest for 5-7 days and then exposed to the second stimulus, either IH or SF, with PSG recorded in an analogous manner.
Results: Both IH and SF were almost 100% effective at inducing arousal when the stimulus occurred with the animal asleep. IH caused significant disruption in sleep during both the light period, when the stimulus was administered, and during the subsequent dark period of normoxia. An initial restriction of NREM sleep during the light phase (from 62 ± 0.5% of light phase at baseline to 44.1 ± 0.5% on day 1 of exposure, $p < 0.05$) and rebound of NREM sleep during the dark phase (from 41.6 ± 1.9% of dark phase at baseline to 54.0 ± 1.5% on day 1 of exposure, $p < 0.05$) returned to baseline levels after five days of IH, but the delta density of NREM sleep remained constantly reduced (to 71.4 ± 6.2% of baseline in light phase and to 83.8 ± 5.8% of baseline in dark phase on day 5). REM sleep was effectively eliminated during the light period with substantial rebound during the dark period. SF induced a cyclical pattern of sleep and arousal that was similar to that of IH. However, the impact of non-hypoxic SF on sleep architecture was generally less severe than for IH. There was no significant decrease in the delta density of NREM sleep and REM sleep continued at close to normal levels

throughout exposure to SF.
Conclusion: Both IH and SF induced a pattern of alternating sleep and arousal that simulated human OSA. However, there was a persistent decline in the depth of NREM sleep and the quantity of REM sleep during IH that was not observed in non-hypoxic SF.

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Sleep Disordered Breathing in Chronic Stroke Survivors. A Long Term Follow-up Study of the SCOPES II Cohort Using Home Based PSG

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Introduction: The prevalence of sleep-disordered breathing (SDB), defined as apnea-hypopnea index [AHI]≥ 5 , in acute stroke patients is between 44-95%, compared to a community prevalence of 9% in adult females and 24% in males. There are limited data beyond 3 months following stroke. The aims of this study were to determine : 1) the prevalence of SDB amongst stroke survivors at 3 years post stroke; 2) the prevalence of sleep apnoea syndrome in this population; and 3) whether known risk factors for SDB correlate with AHI in this population.
Methods: Stroke survivors from the existing SCOPES II cohort, a prospective multi-centre longitudinal cohort study evaluating stroke outcomes in Victoria, completed a sleep disorders questionnaire and if eligible, undertook a home based, sleep study using the Embletta Portable Diagnostic System (Flaga hf, Iceland). All studies were scored by a sleep technician, using modified Chicago criteria
Results: Response rate was 177/217 (65%) with 143 participants eligible for a sleep study. 90/143 (63%) completed a sleep study with 78/90 (83%) producing analysable data. Mean age 66.5 (SD15). Prevalence of SDB (AHI ≥ 5) was 81% (95%CI 72% to 90%). Prevalence at cut offs of AHI ≥ 10, ≥ 15, ≥ 20 and 30 were 45%,35%,18% and 8% respectively. Combined with significant daytime sleepiness (AHI≥5 plus ESS score ≥ 11) prevalence of sleep apnoea syndrome was 20% (95% CI 11% to 29%). AHI correlated with age (ρ = 0.52, P≤ 0.001), systolic BP (ρ=0.26, P=0.026) and daytime sleepiness (ρ=0.27, P=0.019). The adjusted odds for AHI≥15 were 12 times higher for haemorrhagic stroke than for ischaemic stroke: OR = 12.1 (CI=1.4 to 105), p=0.023.
Conclusion: SDB remains prevalent 3 years after stroke. The rate is higher than in the non-age matched healthy community and in most older normal population studies. Age and gender matched case control studies are required

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Self-Reported Sleep Problems in Obese Patients

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Introduction: People individuals have a high prevalence of medical problems including hypertension, diabetes mellitus, and coronary artery disease. While obesity is a known risk factor for obstructive sleep apnea, these patients may be at risk for other sleep disorders as well. Objective: To utilize the Cleveland Sleep Habits Questionnaire to identify patients chronic symptoms that would be associated with a high pretest probability for sleep apnea (OSAHS), restless legs syndrome, narcolepsy, and insomnia in patients with a BMI >40
Methods: Surveys were handed out to patients being evaluated for bariatric surgery at the MetroHealth Medical Center. Items addressed the frequency of snoring behavior, waketime sleepiness or fatigue, and history of obesity/hypertension for composite high risk for sleep apnea (Netzer et al 1999). Several other symptoms were scored as positive vs. negative risk for insomnia, narcolepsy, and restless leg syndrome. Data were also collected regarding demographics and co-morbid conditions. Data were analyzed using SPSS 10 Software (Chicago, Illinois).
Results: 130 consecutive patients completed the questionnaire. Mean age was 33 yrs (range 18 to 64); 34, males; 96 females, mean BMI, 50 (range 35.9 to 80); and Epworth Sleep Scale, 9 (range 1 to 22). 72.3% met high-risk criteria for OSAHS; 41% for insomnia; 23 % for restless legs syndrome; and 5.5% for narcolepsy. A subset of these patients (35) have had sleep studies with a mean AHI 33-events/ hour (Range 5-135-events/ hr). 27% reported use of sleeping pills or bedtime alcohol at least 2-3 times/week. The co-morbid conditions reported include hypertension (41%), diabetes (26%), depression (45%), and asthma (19%).
Conclusion: Morbidly obese individuals, have a high pre-test probability for numerous sleep problems and disorders. These findings highlight the need to obtain a complete sleep history in obese patients undergoing evaluation for sleep apnea. A significant number of these patients also report utilizing sleeping aids.

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The Effects of Treatment for Apnea on Working Memory MR Signal during Functional Magnetic Resonance Imaging (fMRI)

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Introduction: Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) is a serious sleep disorder with associated medical and cognitive consequences. Continuous Positive Airway Pressure (CPAP) is the most commonly used form of treatment for OSAHS and ameliorates some of the cognitive consequences. Despite this, the effects of CPAP on specific brain activity remains unclear. In this study, we examined the MR signal during a working memory task, the 2-back task, OSAHS patients under conditions of treatment and no treatment.
Methods: Five OSAHS patients (mean age 53.6, sd 12.2, 1 woman) were recruited from a larger parent study. All five participants used CPAP for at least 6 hours per night, on average, verified by objective monitoring. All participants practiced the 2-back task to 80% accuracy before entering the scanner. Scanning was conducted under two counterbalanced conditions: (1) after two consecutive nights of treatment and (2) after two consecutive nights without treatment. The 2-back task required participants to detect a stimulus when it was identical to one presented two previous. The task was presented in a blocked design, alternating with a 0-back vigilance task. It consisted of four runs of four cycles. Four 0-back blocks and 2-back blocks were included in every run. Functional images were acquired in the axial plane using contiguous 3 mm slices. BOLD response was detected using a gradient echo-planar pulse sequence with a TR=3840 ms, TE=38 ms, FOV=192 mm. 3D high resolution 1 mm anatomical images were also acquired in the axial plane.

Results: For each voxel in each participant, the BOLD signal during each condition was compared to an ideal wave form that represented stimulus conditions. This resulted in an r-value for each voxel, which was converted to a z-score. Z-scores were thresholded at 3 SDs, to determine regions of activity within each subject, for each condition. Summary maps were created in which the number of participants showing activation was tallied for each voxel in each condition. Frequency maps were thresholded to exclude voxels with a frequency below four. Surviving values were subtracted across conditions to provide an overall map of the relative increase in the number of participants showing activation in any given voxel. Thresholded frequency maps showed that participants recruited expected 2-back-associated regions of interest (ROIs) and that these regions were more active during treatment. A ROI comparison of treatment condition was conducted on the bilateral middle frontal gyri (MFG). Recruited voxels within the ROI were counted for each participant under each condition. These frequencies were compared across conditions using paired t-tests. Significantly more voxels in the MFG showed activation on-treatment ($t = 4.056$, $p < .027$). Greater activation mirrored improvements in performance on the task.
Conclusion: Activation during the 2-back task occurred in the expected brain regions. This activation increased under the condition of active treatment compared to no treatment. Activation enhancement was related to behavioral improvements, but participants were still actively performing the assigned task under the off-treatment condition. CPAP therapy, when not used, may directly affect brain activation as well as performance during cognitive testing.

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Charges for Healthcare Services Before and After Diagnosis of Obstructive Sleep Apnea: A Case-Control Study

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Introduction: Many studies have demonstrated the benefits of treating obstructive sleep apnea (OSA) in terms of quality-of-life and neuropsychological instruments, symptoms, and other indicators, while few have examined the economic costs or benefits of treating OSA. Peker demonstrated that hospitalization days fell in treated patients compared with untreated cases, while Kryger found that OSA patients used twice as many healthcare services as controls during the 10 years prior to diagnosis, and physician claims and hospital days for OSA patients declined significantly after treatment. We further examined this issue using the healthcare charges database of a US-based health maintenance organization (HMO).
Methods: Lovelace Health Systems (LHS) is an integrated healthcare system that includes HMO insurance plans and a 7-bed accredited (>10 years) sleep disorders center. The separate Lovelace Clinic Foundation maintains computerized LHS utilization and enrollment data from 1996 to present. Using this database, all HMO participants (age≥18 years) with OSA first diagnosed between 7/1/99 and 6/30/00 and continuous enrollment from 7/1/97 to 6/30/02 were identified. Three age- and gender-matched controls were also selected for each incident case. Total, inpatient, outpatient, pharmacy, and DME charges for the 2 years before and after OSA diagnosis were computed for each patient and their controls. Sleep disorders-related testing, visits, and DME were excluded.
Results: There were 212 incident cases that met study criteria. Age (mean±SD) was 50.9 ± 10.1 years, 117 (55%) were male, and 125 (59%) were prescribed CPAP. Treatment status did not vary significantly by age or gender, but treated patients had more co-morbidities as assessed by Charlson category (48.8% of treated patients vs. 21.8% of untreated patients had Charlson category ≥ 2.) When categorized by OSA severity using apnea-hypopnea index, treated vs. untreated patients were more likely to have severe OSA (48.0% vs. 9.2%). Typical for healthcare utilization data, charges were not normally distributed and comparisons used medians and nonparametric tests. For the 2 years prior to incident case diagnosis, total charges were double in untreated patients compared with controls ($5128 vs. $2289) and 3 times higher in treated patients ($7535). Total charges remained unchanged for the 2 years after diagnosis in all groups. Median outpatient charges declined $1238/patient after diagnosis in the treated patients, but much less so in the control ($93/patient) and untreated ($203/patient) groups. The disparity between total and outpatient charges was primarily due to pharmaceutical claims, which increased from 26.5% of total charges before to 33.1% after treatment. Median outpatient charge/treated patient declined the most in moderate ($1797), less in severe ($1198) and least in mild ($561) OSA.
Conclusion: Using an intent-to-treat analysis, total healthcare charges are higher in OSA patients compared to controls. Outpatient charges fall significantly when CPAP is prescribed, more so in moderate/severe compared to mild OSA. A 15.8% increase in pharmaceutical charges (Center for Medicare and Medicaid Services data) during the 4 year period of the study likely accounts for the failure of total charges to decline with treatment.

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Prevalence and Annual Incidence of Obstructive Sleep Apnea in a Managed Care Population with Ready Access to Sleep Medicine Services

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Introduction: Healthcare planning requires estimates of disease prevalence and incidence in order to anticipate the future need for resources. Prevalence of obstructive sleep apnea (OSA) from cross-sectional studies (e.g., Wisconsin Cohort Study of middle-aged adults) is 9% in women vs. 24% in men for an elevated apnea hypopnea index (AHI) only, and 2% vs. 4% respectively for OSA with symptoms. The Cleveland Family Study estimated a 5-year incidence of 16% for OSA on the basis of a normal initial home sleep study (AHI<5) followed by an abnormal sleep study at 5 years (AHI≥10) without regard for symptoms. We further examined these issues using the healthcare statistics database of a health maintenance organization (HMO) that operates its own sleep center.
Methods: Lovelace Health Systems (LHS) is an integrated healthcare system that includes HMO insurance plans and a 7-bed accredited (>10 years) sleep center, where sleep physicians consult on all patients referred. The separate Lovelace Clinic Foundation maintains computerized LHS utilization and enrollment data from 1996 to present. All HMO participants (age≥18 years) with OSA first diagnosed between 7/1/99 and 6/30/00 along with continuous HMO enrollment from 7/1/97 to 6/30/02 were identified. Criteria for an incident case were 1) Sleep physician consultation within 6 months of overnight testing; 2) CPT-4 code 95810 or 95811 billed during the incident period; 3) One or more healthcare claims with ICD-9 diagnosis of 780.53 or 780.57 during the incident period; 3) Medical records indicating that OSA was not previ-

ously diagnosed. Criteria for inclusion in the prevalence calculations were 1) Continuous enrollment from 7/1/99 to 6/30/2000; 2) At least one ICD-9 code of 780.53 or 780.57 during the period. The denominator for both was the number of HMO members enrolled during the 12-month incidence period, or 111,468 covered lives.
Results: Age-adjusted prevalence was 160.5 cases/10,000 members, and was higher in males (186.6) then in females (125.3, $p < 0.05$) for all age groups except 55-64 years. Male/female prevalence increased progressively with age except for 85+ years, ranging from 35.7/20.0 for age 18-24 up to 304.0/155.9 for 75-84 years. There were 212 incident cases identified during the study period, yielding an overall unadjusted annual incidence of 19.0 per 10,000, or 0.19%. Male incidence was 22.5 and female incidence was 16.0 per 10,000.
Conclusion: Data from our cohort yield prevalence estimates for OSA that are similar to those determined by a cross-sectional study for symptomatic individuals and much lower than for all patients with OSA. Similarly, our annual incidence is much lower than that determined prospectively by the Cleveland Family Study (3.2%/year) for a laboratory diagnosis of OSA regardless of symptoms. These data suggest that, not surprisingly, physicians refer for sleep apnea testing only when sleepiness or other symptoms exist. However, the lack of strict concordance between AHI and daytime sleepiness in OSA is well known, while increasing evidence links adverse cardiovascular outcomes with higher AHI regardless of symptoms. Development of more robust, evidence-based criteria for sleep disorders referral is needed.

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Sham-CPAP Use Prior To CPAP Treatment Is Associated With Better Compliance In Alzheimer's Disease

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Introduction: Obstructive sleep apnea (OSA) is a prevalent condition, especially in elderly, with potentially serious medical and psychosocial consequences. Nasal continuous positive airway pressure (CPAP) is the treatment-of-choice and has been shown to reduce the frequency of nocturnal respiratory events, improve sleep architecture and decrease daytime sleepiness. However, patient compliance with CPAP is relatively low. This pilot study is part of a larger study evaluating the effect of CPAP on cognitive functioning in patients with dementia and OSA during a 6-week period. Half the patients used sham-CPAP the first three weeks and real CPAP the second three weeks (SHAM). The other half had real CPAP for all six weeks (REAL). This analysis was aimed at comparing compliance of the two groups and at comparing patients who continued using CPAP after the end of the study to those who did not in terms of their previous compliance.
Methods: Data from 20 patients with mild Alzheimer's disease (AD) are included in this preliminary analysis (18 men, 2 women, mean age=78.65, SD=7.8). At least one month after termination of the study, patients were asked whether they obtained a CPAP machine through their health insurance company and whether they continued to use it. T-tests were used: a) to compare compliance during the last three weeks of the study in SHAM vs. REAL and b) to compare patients who continued using CPAP after the end of the study to those who discontinued CPAP, based on the number of hours of CPAP use in the last three weeks of the study.
Results: When the number of hours of CPAP use during the second three weeks for each group was compared, the SHAM group (n=9) averaged 5.0 hours a night (SD 2.3) during the second three weeks while the REAL group (n=11) averaged 3.1 hours a night (SD 2.3) during their second three weeks ($t(58)=3.02$, $p=0.0038$). Continuation of CPAP treatment after the end of the study was also related to compliance during second three weeks, such that patients who showed higher compliance during treatment were more likely to continue using the machine after the termination of the study ($t(58)=p=0.0004$).
Conclusion: Patients with AD and OSA were able to tolerate CPAP. The difference between the groups in the number of hours of CPAP use was not only statistically significant, but with two hours more per night of CPAP use, also very clinically significant. Giving patients time to adjust to wearing the mask resulted in the CPAP being worn for a greater number of hours each night. Starting patients off with a mask and machine with little or no pressure might make it easier for them to tolerate real CPAP for longer time periods thus improving compliance. Studies need to examine how many days at low pressure are necessary for improved compliance. In addition, these findings need to be replicated in non-demented adults.

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Arousal Detection By Analysis Of Autonomic Markers In Sleep Disordered Breathing

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Introduction: Repetitive arousals are linked to the consequences of sleep apnea syndrome (SAS) but visual analysis of arousals is time consuming and observer dependant. Autonomic markers such as vascular peripheral tone may be better related to the pathophysiology of SAS. Therefore an automated analysis of autonomic markers is desirable. The aim of this study was to compare arousal detection by automated analysis of peripheral arterial tonometry (PAT), digital oximeter pulse waveform (PLE and PLA) and pulse transit time (PTT).
Methods: 7 patients (6 M, 42 to 64 yrs, BMI 22 to 34 kg/m2) were recorded during one night by PSG on a Cidelec system including sampling of PAT (Itamar Medical, Haifa, Israel) and oximetry (BCI, Waukesha, WI, USA). Apnea-hypopnea range was 6 to 90/hr. Visual arousal analysis (VAr) have been made according the ASSM criteria (Sleep 1999, 22: 667-689). PLE was defined as the oximeter pulse waveform range computed every second. PLA was the average of max and min pulse waveform for each cardiac cycle. Pulse Transit Time (PTT) was computed from ECG and pulse waveform of the oximeter. Receiver Operating Curves (ROC) have been computed for VAr as the gold standard vs. PAT, PLE, PLA and PTT signals optimising for the best threshold and lagtime between arousal and signals. Data have been computed in the INRIA Scilab-Scicos scientific environnement (http://scilabsoft.inria.fr/) and compared by one way ANOVA.
Results: The areas under the curve (AUC) from the ROC analysis of autonomic markers vs. visual arousal as the gold standard are significantly different ($p<0.01$). The diagnostic value of PAT (AUC mean=0.84, SD=0.06) is better than that of PLA (0.78, 0.06) and PTT (0.76,0.04) ($p<0.05$). AUC for PLE(0.81, 0.05), PLA and PTT are not statistically different. All signals were delayed compared to VAr : 4 sec for PAT, 2.9 sec for PLE, 2.7 sec for PLA and 3 sec for PTT.
Conclusion: Peripheral arterial tonometry (PAT) and the range of the oximeter pulse waveform signal (PLA) are the most reliable to detect arousals in sleep disordered breathing. Pulse transit time (PTT) and

oximeter pulse waveform average (PLA) have a lower diagnostic value.

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Body Position and Periodic Breathing in Heart Failure

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Introduction: Periodic (Cheyne-Stokes) breathing affects 30-40% of patients with heart failure. It has been reported to be more common in men, older subjects, subjects with atrial fibrillation and hypocapnia. The effect of body position on periodic breathing is unknown. The purpose of this study was to evaluate the frequency of periodic breathing in different body positions in a consecutive sample of heart failure patients.
Methods: Seventy-nine consecutive subjects followed at the heart failure clinic, Heart Institute, University of Sao Paulo, Brazil, underwent history, physical examination, assessment of subjective sleepiness (Epworth Sleepiness Scale), arterial blood gases and overnight polysomnography (EMBLA). All subjects had Ejection Fraction (EF) < 50%. During PSG airflow was measured using a thermistor and a pressure cannula; respiratory effort was measured using piezo-electric bands. PSG was scored according to R&K criteria. Central apneas were defined by the absence of airflow associated with an absence of thoracic and abdominal movements lasting at least 10 seconds. Central hypopneas were defined as a reduction in airflow by at least 50% from baseline and absence of thoracic and abdominal movements lasting at least 10 seconds. Periodic breathing was defined as crescendo-decrescendo pattern of breathing: central apneas or hypopneas followed by progressive hyperpnea. Central apnea-hypopnea index (AHI) over 5 was defined as significant and was determined in NREM sleep in various body positions. Central AHI in different body positions was compared using one-way ANOVA. Data are presented as means and standard deviations. P value of <0.05 was considered significant. The study was approved by the local Ethics Committee; all subjects gave informed consent prior to participation in the study.
Results: 79 subjects (51 males, age 59.2 ± 11.4 years, BMI 25.8 ± 4.9, EF 35.5 ± 6.0 %, Epworth 10.7 ± 5.7) were enrolled. Periodic breathing (AHI>5) was diagnosed in 22/79 subjects (27.9%), AHI > 15 in 16/79 (20.3%). Thirteen subjects slept in more than one position; six (46%) had the highest AHI in the supine position, five (36%) in left decubitus position, one in right decubitus position and one in prone position. The mean central AHI was 30.8, 29.3, 20.3, 37.6 in supine, left, right and prone positions respectively. There was no significant difference in central AHI in NREM between different positions. Five subjects (38%)had worsening of periodic breathing in supine NREM sleep (defined as central AHI > 15 supine and AHI < 15 non-supine and supine AHI/ non-supine AHI > 2.0), however all these subjects also had obstructive sleep apnea.
Conclusion: Periodic breathing is common in Brazilian heart failure patients. There was no significant effect of body position on mean central AHI in this population. Approximately 38% of subjects with Cheyne-Stokes respiration had positional periodic breathing, worse in supine sleep,however,all these subjects also had OSA suggesting that positional changes in upper airway may have destabilizing effect on periodic breathing.

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Snoring Control Using a New Tongue-Retaining Type Oral Appliance

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Introduction: Snoring is reported by more than 35% of the adult population according to “Sleep In America 2000”. When snoring is without apnea or OSA<10, it is frequently treated with an oral appliance. These are of two major types: those that keep the tongue from retro-lapsing by suction (TRD) and those that move the mandible forward mechanically (MAD). Recent reports of long term effects of MADs implicate permanent changes in bite and/or joint pain. TRDs have been employed less frequently by dentists as they are not custom fit and not titratable. A new appliance of the TRD type, constructed from a patient’s impression, has a unique design with an interior shelf to capture the tongue by suction. Developed by Dr. Sue, called the NB/HS, it enforces nasal breathing. It is FDA approved. A test of it’s effectiveness in a small group of non-apneaic snorers approved by the IRB is underway.
Methods: To date ten subjects previously cleared of OSA by PSG studies have signed informed consent and are wearing the device. Subjects are then tested for two consecutive nights by home monitoring using Vitaport equipment which prints out sleep stages, SaO2, sleep position, and snoring data. Subjects sleep one night without the appliance and one with it in place all night. Questionnaires are completed on frequency of use, comfort, sleepiness (ESS). Bed partner rates snoring degree with and without the device. Subjects are all males, ages 33-62 Mean=48.6, Weight Mean= 238.7lb.
Results: Study still in progress. Seven subjects have completed of which five show marked decrease in percent sleep time with snoring (number of sleep epochs with snores on nights with versus nights without the device).Successful cases dropped from Mean=40.36% time snoring to Mean=18.7%. Failures had 50.5% without the device and 55.5% with it in place. On a ten point scale, the bed partner rated degree of snoring without treatment Mean=8.66, with treatment Mean=3.5. Even two unsuccessful cases by PSG counts improved by spouse report to 4, and 5. Compliance was self-reported by 4 of the successful cases to be “using the device all night every night”. The other successful case reported using it “every night for a few hours”. Unsuccessful cases reported less frequent use.
Conclusion: To date, 71.4% of non-apneaic snorers were successfully treated by a new appliance of the TRD type. The two unsuccessful cases showed no difference in their snoring by sleep position. Snorers who snore substantially less in lateral sleep are likely to be improved using this device.

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A New Approach to Nasal CPAP Therapy in Obstructive Sleep Apnea (OSA) Using High Flows of Warmed and Humidified Air

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Introduction: Mask problems with nasal CPAP therapy include pressure on the face, bulkiness, appearance and drying of the upper airway mucosa. A humidified CPAP system and high flow nasal cannula which exerts its effect by pressurizing the nasopharygeal airway, delivered through small-bore flexible tubing and a nasal cannula not unlike that used in standard low-flow oxygen therapy, offers an alternative to these problems.
Methods: The safety and efficacy of a high airflow cannula system, ComfortAire (CA)*, was studied in 16 adult male patients with mild-to-

moderate OSA, whose apnea-hypopnea indices (AHI) were between 8-40 episodes per hour, with body mass indices (BMI) of 26-37 kg/m2, and who had untreated baseline oxygen saturation levels (SpO2) between 64-87%. Each patient had undergone baseline polysomnography and CPAP titration studies on two previous separate nights. If the CPAP titration had not been done within 3 months of the CA study, or if there had been a weight change > 10 pounds, the CPAP calibration study was repeated. On a third night an CA flow titration was performed, with the sleep technician slowly increasing the flow of air up to 60 lpm until periods of oxygen desaturation < 88% were minimized. AHI, SpO2 nadir measured at "best" CA flow and "best" CPAP pressure, total sleep time and minutes of REM sleep achieved, and subject evaluation comments were compared for the two systems. Neither subjects, PSG scorers, nor the investigators were blinded for the study.

Results: Two patients were dropped from the study due to their inability to sleep during either the CPAP or CA titration studies. For the 14 subjects, the mean AHI at baseline was 23.4 episodes per hour; at "best" CPAP 2.1 episodes per hour; and on the CA at optimum flow, 6.5 episodes per hour. The mean nadir of SpO2 at baseline was 79.8%; at "best" CPAP it was 93%; and on CA it was 90.0%. Mean "best" CPAP was 7.1 cm. H2O and mean optimal CA flow was 47 LPM. The mean total sleep time (TST) at baseline was 5.81 hours; on CPAP it was 5.25 hours; and on CA it was 4.33 hours. Mean REM duration in the baseline PSG totaled 54 minutes; on CPAP it was 48 minutes, and on CA it was 28.5 minutes. Of 12 patients who answered a summary question regarding their impression of the device, eight preferred the CA after one night of use. ANOVAs on sleep data for 14 subjects who have already completed all study conditions, showed that TST was significantly shorter for the CA night (4.3 hrs) compared to diagnostic and CPAP nights (5.9 and 5.2 hrs. respectively) ($p<.001$). Sleep efficiency was significantly different among all conditions with diagnostic>CPAP>CA nights ($p<.001$). Percent stage 1 sleep did not differ significantly among conditions. The percent of REM sleep was significantly greater for the diagnostic night than the CA night ($p<.001$). AHI did not differ between CPAP and CA nights (2.0 and 7.3) but was significantly lower then the diagnostic night (28.9) ($p<.001$). The lowest oxygen saturation was significantly lower on the diagnostic night compared to CPAP and CA nights (79%, 92% and, 90% respectively) ($p<.001$).

Conclusion: We evaluated the safety and efficacy of a new CPAP system that delivers high flows of heated humidified air through a small bore, double-pronged nasal cannula. In subjects with mild-to-moderate OSA, the CA reduced the AHI to within near-normal levels, and ensured adequate oxygenation (SpO2 > 88%) in 13 of 15 patients. Further studies will determine whether or not the CA has a durable effect on sleep architecture.

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Clinical Practice among Non-Sleep Specialist Physicians When Sleep Apnea is Suspected

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Introduction: Physicians in practice frequently encounter patients with sleep apnea. Obstructive sleep apnea occurs in 4% of men and 2% of women age 30-60, and can have significant medical, economic, and social consequences. In order to diagnose patients with sleep apnea, NSSPs must initiate an appropriate evaluation when apnea is suspected. This study reports NSSPs responses in such cases.

Methods: 770 NSSPs were identified by databases of active staff of a teaching hospital and faculty of University of Illinois College of Medicine at Peoria. Subjects responded anonymously to a survey sent by U.S. mail. Questions were objective (multiple choice) except those regarding demographic data.

Results: One hundred thirty-nine subjects responded (18.1%). Subjects were asked: When you first suspect a patient in your practice has sleep apnea, do you usually (check only one). Seventy-four primary care physicians (PCPs) and 45 specialists responded. Response rates for each option were as follows (noted as PCPs, Specialists): Order a sleep test; 33 (44.6%), 10 (22.2%); Refer to a sleep specialist for consultation, 12 (16.2%), 14 (31.1%); Refer to ENT for a consultation, 5 (6.8%), 0; Order overnight pulse oximetry, 4 (5.4%), 1 (2.2%); Have the patients spouse/bedpartner observe for apnea while the patient sleeps, 12 (16.2%), 4 (8.9%); Advise the patient to lose weight, 3(4.1%), 2 (4.4%); Wait to see if the problem resolves, 1 (1.4%), 0; and Wait for later visits to address the problem, 0, 0. Other 4 (5.4%) and 14 (31.1%). The difference between PCPs and specialists was significant in 2 of the responses: Order a sleep test and Other (Pearson Chi-Square = 24.393, $p=0.001$). All written explanations for a response of Other described referral back to the primary care physician. Subjects were also asked: If you have asked the patients spouse/bedpartner/parent to observe for apnea while the patient sleeps, and no apnea is observed, do you usually (check one). Sixty-two PCPs and 29 specialists responded as follows (noted as PCPs, Specialists): Order a sleep test (28 [45.2%], 6 [20.7%]); Refer to a sleep specialist for consultation (12 [19.4%] PCPs, 14 [48.3%] specialists); Refer to ENT for consultation (0, 1 [3.4%]), Order overnight pulse oximetry (5 [8.1%], Advise the patient to lose weight (3 [4.8%], 1 [3.4%]), Wait to see if the problem resolves (7 [11.3%], 1 [3.4%]), Wait for later visits to address the problem (5 [8.1%], 0), Take no further action (2 [3.2%], 1 [3.4%], and Other (0, 5 [17.2]). There was a significant difference between PCPs and specialists (Pearson Chi-Square=27.928, $p<0.0005$) in responses to Order a sleep test and Refer to a sleep specialist for consultation.

Conclusion: Ideally, NSSPs should be able to respond appropriately (order a sleep test or sleep consultation) when apnea is suspected. Although the majority of subjects selected these responses, 42% chose other options, and 34% chose other options if a witness who was asked to observe for apnea saw none. This study demonstrates a need for increased knowledge of appropriate work up for sleep apnea among NSSPs.

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Relative Theta Power Reflects Specific Cognitive Deficits In Moderate To Severe Obstructive Sleep Apnea Syndrome

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Introduction: Obstructive Sleep Apnea Syndrome (OSAS) causes both hypoxemia and sleep fragmentation resulting in excessive daytime sleepiness (EDS), which lead to cognitive deficits. Executive and psychomotor tasks have been suggested to be affected in OSAS patients and have been associated to nocturnal hypoxemia (Bedard et al., 1991). Hypoxemia has been shown to correlate with changes in waking quantitative EEG more so than EDS (Morisson et al., 1998). The aim of the present study was to evaluate the relationship between quantitative EEG and performance on neuropsychological tests of executive and psychomotor functions in moderate to severe OSAS patients.

Methods: 13 men with OSAS (54.46 (4.96) years old) with a minimal desaturation under 90%, underwent a standard all-night polysomnographic evaluation followed by a waking EEG (10 min/eyes closed). A total of 96 sec of artifact-free EEG were subjected to spectral analysis using FFT on 4 sec epochs with a resolution of 0.25 Hz and cosine tapering. As a measure of cortical slowing, the relative theta power (4.00 to 8.00 Hz) was quantified in all regions. Executive fonctions were assessed by the Maze, Mirror Tracing, Trail A and B and Purdue Pegboard tests. The relationship between variables was assessed by Spearman correlation tests.
Results: Patients were moderate to severely affected : AHI of 42.09 (13.2), minimal desaturation of 73.73 (11.2) % and BMI of 34.8 (7.1). They had sleep disruption : index of micro-arousals of 29.58 (19.2), sleep efficacity of 83.31 (2.3) %, stage 1 of 17.11 (7.8) %, stage 2 of 66.64 (9) %, SWS of 1.88 (3.2) % and REM sleep of 14.34 (5.4) %. Executive and psychomotor deficits were significantly correlated with the total relative theta activity : Purdue Pegboard executed with the domin0ant hand (r=0.79) (p=0.001), for both hands simultaneously (r=0.73) (p=0.004), with the non-dominant hand (r=0.68) (p=0.010) and the Maze test (r=0.62) (p=0.02). The relationship between theta power and Mirror Tracing, Trail A and B did not reach statistical significance. There was a relationship (or a trend) between the index of micro-arousals on one hand and errors made at Trail A (r=0.65) (p=0.02), Maze test (r=0.55) (p=0.05), Purdue Pegboard executed with the dominant hand (r=0.48) (p=0.09) and Purdue Pegboard executed with both hands (r=0.63) (p=0.02). There was no correlation between hypoxemia measures and theta power or neuropsychological tests except for a trend between minimal saturation and errors made at the Maze tests (r=0.50) (p=0.07).
Conclusion: The waking EEG seemed to be an interesting measure for analysing specific variations in cognitive deficits. Sleep fragmentation but also nocturnal hypoxemia may differentially contribute to the cognitive dysfunctions observed in OSAS patients. The next step will be to assess the relationship between theta activity in different cortical regions and specific cognitive deficits.

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Risk Factors Of Sleep-Disordered Breathing In A Brooklyn-Based Caribbean Sample

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Introduction: Sleep-disordered breathing (SDB) is a potentially life-threatening condition. According to a population-based study of adult Americans (40 - 60 years), rates of SDB were much higher among minority groups, with estimates of 16.3% of ethnic minorities having greater ≥ 20 RDI as compared to 4.9% of non-Hispanic Whites. Additionally, a case-control family study comparing Blacks and Whites (2 - 86 years), found that 31% of Blacks versus 10% of Whites had RDI greater than 10. Blacks are at increased risk for developing SDB independently of age, sex, and body mass index. This study assessed the prevalence of SDB risk factors in a Caribbean community in Brooklyn.
Methods: Questionnaires were distributed in three primary-care settings serving primarily individuals of Caribbean descent. A bilingual investigator provided assistance to volunteers agreeing to participate in this study and collected responses from each clinic. A total of 554 patients volunteered (ages: 20-90 years, mean = 48.17 ± 16.75; women = 55% and men = 45%), of which 95% provided valid data. All data were entered in SPSS 10.0 for statistical analysis.
Results: Prevalence of SDB symptoms was: snoring (45%), gasping and choking at night (11%), breathing pauses (11%), witnessed snoring and breathing arrests (36%), and excessive daytime sleepiness (33%). Some reported falling asleep while watching television (47%) or while driving (14%). Thirty-four percent reported difficulty initiating sleep (DIS), 34% difficulty maintaining sleep (DMS), and 44% early morning awakenings (EMA); 35% indicated daytime napping and 11% used sleep medicine. Most (87%) rated their sleep satisfaction as good to excellent, and 13% as fair to poor. Overall, 64% rated their health status as good to excellent; 36% as fair to poor. Of the sample, 35% reported a history of high blood pressure (HBP), 44% a family history of HBP, and 15% a history of heart problems. Twenty-three percent indicated that they were not sad in the past month, 53% sometimes, and 24% often. Thirty-four percent reported difficulty concentrating, and 20% indicated morning headaches. The average patient had a BMI of 29.15 ± 7.16kg/m2 and slept 6.45 ± 1.88hrs habitually. Both men and women with a BMI >= 30kg/m2 reported greater snoring rates (42% vs. 51%, $\chi 2 = 7.84$, $p < 0.01$), HBP (29% vs. 43%, $\chi 2 = 9.97$, $p < 0.05$), and family history of HBP (40% vs. 51%, $\chi 2 = 5.14$, $p < 0.05$).
Conclusion: In contrast to combined 2002 and 2003 NSF data that 34% of American adults (ages 18 - 84 years) reported snoring, 8% breathing pauses, and 26% excessive daytime sleepiness, our results showed that 45% of the sample reported snoring, 11% breathing pauses, and 33% daytime sleepiness. Furthermore, according to national data 22% reported DIS, 35% DMS, and 24% EMA. In our sample, 34% reported DIS, 34% DMS, and 44% EMA. Paradoxically, while individuals in our study reported greater rates of SDB symptoms and sleep complaints, most were satisfied with their sleep. Conceivably, sleep-related problems might be perceived differently in that community.

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Continuing Use Of CPAP In Alzheimer's Patients: Relation To Depression

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Introduction: Sleep Disordered Breathing (SDB) is quite common in patients with Alzheimer's disease (AD). We have previously evaluated CPAP compliance in these patients and found that on average AD patients were using CPAP about 5.36 hours a night. The current analysis is part of a larger randomized, double blind, placebo-controlled study evaluating the effect of CPAP on cognitive functioning in patients with dementia and SDB and is aimed at examining the correlations between CPAP continuation and initial sleep and mood.
Methods: Neuropsychological testing was administered before the start of treatment, after three weeks, and after six weeks of CPAP treatment. All patients had home polysomnography (PSG) (Embla, Medcare) and completed the following questionnaires: Pittsburgh Sleep Quality Inventory (PSQI), Functional Outcome of Sleep Questionnaire (FOS-Q), the Cornell Depression Scale and Epworth Sleepiness Scale (ESS). Data from 20 patients with mild AD are included in this preliminary analysis (18 men, 2 women, mean age=78.65, SD=7.8). After termination of the study, patients were asked whether they obtained a CPAP machine through their health insurance company. Student t-tests were calculated to compare the 7 patients who obtained CPAP machine and continued using it after study termination to the 13 who did not. The groups were

compared on their initial sleep and questionnaires scores.
Results: No demographic differences (age, gender, race, ethnicity) were found between the patients who continued using CPAP and those who did not. Similarly, the two groups did not differ in their initial PSG parameters, on severity of sleep apnea or on reports of subjective sleepiness (ESS). However, those who continued using CPAP were significantly less depressed (1.867 mean Cornell score; SD 2.03) than those who did not (5.615 mean Cornell score; SD=4.01)(t(18)=2.304, p=0.03).
Conclusion: These results showed that patients who were more likely to obtain and continue using CPAP were less depressed. This may suggest that mood may be an important factor determining CPAP compliance and long-term use. Further research may enable the determination of the role of caregivers and the relationship between the patient and his/her caregiver in the decision to obtain the CPAP and in continued CPAP usage.

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Body Mass Index Predicts Fatigue in Obstructive Sleep Apnea Patients

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Introduction: Fatigue, obesity and obstructive sleep apnea (OSA) are tightly entwined. Fatigue is a common complaint in OSA patients, obesity is a major risk factor for OSA, and fatigue is often a complaint in the obese regardless of the presence of OSA. Although OSA, obesity, and fatigue have been important objects of study, there are surprisingly few studies that have examined the relationship between fatigue and obesity in OSA patients after controlling for disease severity. This study examined if obesity, as measured by body mass index (BMI), would account for a significant portion of the fatigue experienced by patients with OSA after controlling for disease severity [respiratory disturbance index (RDI) and percent of time spent at an oxyhemoglobin saturation below 90% (SpO290%)].
Methods: Fifty-eight patients (11 women and 47 men) with moderate to severe OSA (RDI ≥ 15) between the ages of 30 and 65 participated. Participants had their height and weight measured to calculate BMI (kg/m2), underwent an overnight polysomnogram, and completed the fatigue subscale of the Profile of Mood States (POMS). Data were analyzed with Pearson's correlations, hierarchical linear regression, and analysis of covariance (ANCOVA) using SPSS 11.0 software.
Results: The RDI (r=0.626, p<.001) and SpO290% (r=.471, p<.001) showed significant univariate associations with BMI. The RDI (r=0.290, p=.027), SpO290% (r=.368, p=.004) and BMI (r=.457, p=.000) were also significantly correlated with POMS fatigue. We then analyzed these data with hierarchical linear regression to ascertain if BMI contributed additional information to POMS fatigue beyond that explained by OSA severity. The score on RDI and SpO290% together accounted for 14.6% of the variance in the POMS fatigue score (p=.013). Next, after controlling for these factors, BMI significantly accounted for an additional 9.8% of variance in POMS fatigue (p=.002).
Conclusion: This study suggested that BMI, after controlling for the OSA severity, was significantly associated with fatigue in OSA patients. From a clinical perspective, the assessment and treatment of overweight, not just treatment of the disordered breathing itself, might reduce the fatigue experienced by patients with OSA.

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Comparison of a Portable Device based on Peripheral Arterial Tonometry to Standard Level 3 Cardiopulmonary Screening for Obstructive Sleep Apnea in a VA Medical Center Population

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Introduction: Obstructive Sleep Apnea (OSA) is a common disorder that presents a large burden on the VA Healthcare system. Ambulatory screening for OSA has allowed our VA sleep lab to reduce long waiting times for standard diagnostic tests. We compared a portable device based on Peripheral Arterial Tone (PAT) with an established cardio-pulmonary level 3 device.
Methods: Retrospective review of patients who underwent simultaneous Watch-PAT (WP100) and Edentrace (ET) screening for OSA. WP100 records included PAT signal, heart rate, oxygen saturations and wrist actigraphy. Edentrace records included heart rate, oxygen saturation, chest impedance, airflow, body position and snoring. For each patient, the two studies were scored automatically according to proprietary software and many indices were calculated: PAT Respiratory Disturbance Index (PRDI), PAT Oxygen Desaturation Index 4% (ODI4), Apnea-Hypopnea Index using 4% saturation drop (ET-AHI) and ET-AHI corrected by actigraphically derived total sleep time (ET-AHI/WP time). These values were compared for the 2 studies using linear regression and Bland-Altman plots. 18 of the study patients were randomly selected and 105 five-minute epochs were then compared. All events were logged in time sequence. They were defined by the Edentrace as apneas (central, obstructive and mixed), hypopneas, periodic heart rate variability events or normal and then compared to Watch-PAT events that were defined as respiratory event or normal. Results are presented as mean ± standard deviation. Statistical significance was considered to be present when $p < 0.05$.
Results: The study included 56 subjects with only two females (age 59.3 ± 11.3 years, BMI 32.9 ± 7.8 kg/m2 and Epworth Sleepiness Score 12.8 ± 4.5). The study population had a PRDI (37.1 ± 22 events/hr), ODI4 (13.19 ± 21.7), ET-AHI (18.6 ± 15.5) and ET-AHI/WP time (27.9 ± 26). Using linear regression analysis there were significant correlations between PRDI and ET-AHI ($r = 0.53$, $p<0.0001$), PRDI and ET-AHI/WP time (r 0.56, $p<0.0001$), ODI4 and ET-AHI ($r = 0.67$, $p<0.0001$), and ODI4 and ET-AHI/WP time ($r = 0.70$, $p<0.0001$). Twenty-two of the 105 epochs compared were scored normal by both devices. Edentrace scored 15 more epochs as normal, but revealed 83 episodes of cyclic & repetitive heart rate variability of which 61 (73%) respiratory events were recorded by WP100. Of all the events on ET, 68% of central apneas, 80% of obstructive apneas, 50% of hypopneas and 65% of mixed apneas were detected by WP100. 98% of the events not detected by the WP100 were due to periods of movement-related "wake (activity)".
Conclusion: Based on these results, the WP100 compares well with a Standard Level 3 Cardio-pulmonary screening study for OSA. This device is simple to use and its ability to discriminate "wake" from sleep (rest activity cycle) provides better accuracy for severity assessment of OSA. The WP100 is better in detecting non-apneic respiratory events (NARE), but can miss some apneic events due to movement-related wake designation by the actigraphy. The advantages of each device seem to be complimentary for evaluation of patients with sleep-related breathing disorders.

Equipment provided by Itamar Medical Ltd.

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Home Screening Device For Follow-Up Of Continuous Positive Airway Pressure Therapy In Patients With Obstructive Sleep Apnea Syndrome

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Introduction: The continuous positive airway pressure (CPAP) is accepted as a primary therapy for patients with obstructive sleep apnea syndrome (OSAS). However, the compliance of CPAP therapy is 60-80% and various side-effects occur during CPAP therapy, for instance, mouth dryness, nasal obstruction and air leak form nasal mask. New home screening device (LT-200 Fukuda Denshi, Tokyo, Japan) could be recorded for consecutive three days, and provide an information based on both body positions and breathing conditions during sleep. We therefore investigated the usefulness of LT-200 for follow-up of OSAS.

Methods: Fifteen patients (mean age 49.4±10.5 years, body mass index 24.6±4.1 kg/cm2, Epworth sleepiness scale 10.0±6.5) were enrolled in this study. Standard polysomnography (PSG) and home screening were performed for all patients to diagnose OSAS and determine an appropriate level of CPAP. Moreover, all patients underwent home screening using LT-200 after the treatment for three months with CPAP; the procedure was performed on three consecutive nights for patients, the first night during natural sleep, and both second and third nights during treatment with CPAP. The number of apnea/hypopnea episodes per hour (apnea-hypopnea index:AHI) and the total time that nocturnal oxygen saturation was <90% (oxygen desaturation time:ODT) were measured. We investigated that the relations the severity of OSAS using PSG and LT-200 and the improvement of OSAS by CPAP therapy. Furthermore, AHI at each body position with LT-200 was calculated to evaluate the efficacy of the lateral sleep position. Data were presented as mean ± standard deviation and were analyzed by ANOVA. A probability value less than 0.05 was considered statistically significant.

Results: Both AHI and ODT in all patients significantly decreased on the night they received treatment with CPAP. AHI using LT-200 was significantly correlated with those using PSG ($r=0.89$, $p<0.0001$). There was no significant correlation in ODT between PSG and LT-200. AHI using LT-200 on the second day of CPAP therapy significantly decreased than that at natural night (5.1±7.4 vs 22.0±16.4 /h, $p<0.05$). Both AHI and ODT at the second day of CPAP therapy had tendency to decrease than those at the first day. AHI on right and left lateral sleep positions was significantly lower than that on spine position (4.3±5.1, 9.3±10.1 vs 32.1±15.7/h, respectively, $p<0.05$).

Conclusion: Our results suggest that home screening test using LT-200 is reliable, and provides an important information about both body positions and breathing conditions during sleep. It should therefore prove to be a useful tool in the follow-up of patients with OSAS.

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Inspiratory Flow Limitation During NREM And REM Sleep Investigated Under CPAP And C-Flex Conditions

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Introduction: Nasal CPAP is the current therapy of choice in sleep related breathing disorders. The CPAP pressure is usually a fixed pressure for inspiration and expiration. However, nCPAP therapy has a limited compliance even in patients who require this therapy due to a high quantity of apneas and hypopneas. The recently introduced PAP system with C-flex (REMstar Pro) intends to improve this situation by lowering the expiratory pressure proportional to the patient's airflow. Three different gain values for the proportional reduction of pressure during expiration correspond to three different C-flex modes. Since the pressure is lowered adaptively we wanted to investigate the occurrence of flow limitations during inspiration in different sleep stages using the three possible C-flex modes.

Methods: Subjects with an AHI > 20/hour were included in this study. Patients underwent cardiorespiratory polysomnography with added recording of respiratory flow (pneumotachograph and pressure transducer by Hans Rudolph) and respiratory effort (esophageal pressure transducer by Gaeltec). Effective pressure was titrated using the CPAP mode. Subsequently the CPAP mode and the three C-flex modes were used in a randomized order. The four conditions were applied during NREM sleep for continuous episodes of 15 minutes each. The four conditions were also applied during REM sleep. Since REM sleep episodes tend to be shorter, five continuous minutes were taken as one episode. Then three episodes of these five minutes of REM sleep were recorded for each of the four ventilation conditions in order to balance the number of breaths in REM and NREM sleep. A total of 120 minutes were used for subsequent evaluation. Breath by breath evaluation was performed with the Windaq software (Dataq Instruments, OH, USA). Inspiratory flow limitation was counted for all breaths if the amplitude of esophageal pressure exceeded a fixed value, calculated for each subject during quiet wakefulness as the mean esophageal pressure amplitude plus two-fold standard deviation.

Results: Four subjects were recorded with full 120 minutes of valid and artifact free signals for esophageal pressure, airflow and polysomnography and with all four conditions for NREM and REM sleep. A total of 7116 breaths were evaluated. 223 breaths (3.1%) had inspiratory flow limitation according to our criteria. 117 of these breaths (52%) occurred during CPAP mode and 106 (48%) occurred during the three C-flex modes. During NREM sleep we found again 117 breaths (52%) and during REM sleep 106 breaths (48%) were detected. One of the four subjects had most flow limited breaths (162). In this subject 93 breaths occurred during CPAP mode and 69 during C-flex mode.

Conclusion: The results confirm that most flow limited breaths are found in subjects which do snore even when having effective CPAP therapy. During the sum of all three C-flex modes we do see less flow limited breaths than during the CPAP mode. Therefore we summarize that there are no signs of an increased number of flow limitations during C-flex compared to CPAP mode. However, the number of subjects under this protocol has to be increased in order to obtain considerable statistical strength for our results.

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The Incidence Of Glucose Intolerance In Patients With Obstructive Sleep Apnea-Hypopnea Was 62.4%

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Introduction: Although obstructive sleep apnea syndrome (OSAS) and non-insulin dependent diabetes mellitus (NIDDM) are both associated with coronary risk factors, particularly obesity, it was still unclear which values predict glucose intolerance in OSAS. This study was aimed to clarify the relationship by the OGTT performed on Japanese OSAS patients.
Methods: In the early morning after polysomnography, we performed an oral glucose tolerance test (OGTT; 75g) on 73 men with an apnea-hypopnea index (AHI)<5 (control group), and 679 OSAS patients (AHI>5) without treated diabetes mellitus. The OSAS patients were classified by AHI level into four groups and by body mass index (BMI) level into three groups.
Results: The incidence of NIDDM in the 679 OSAS patients was significantly higher than that of the control group (25.9% vs. 8.2%, p<0.001). Among the OSAS patients, 424 patients (62.4%) were diagnosed as having impaired glucose tolerance or NIDDM. We compared measurements of glucose tolerance (fasting PG, fasting IRI, HbA1c and HOMA-IR) in groups that divided using AHI and BMI categories. These measurements were likely to have more relevant BMI than AHI. Furthermore, we calculated using logistic regression analysis in 679 OSAS patients whether any of the measured independent variables (age, Apnea-hypopnea index, minimum SpO2 and body mass index) might predict glucose intolerance (HOMA-IR>3) with OSAS.
Conclusion: The glucose intolerance in OSAS patients was only predicted by BMI.

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Nocturnal Overdrive Pacing Does Not Reduce Apneas and Hypopneas in Pacemaker Patients

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Introduction: Sleep Apnea Syndrome (SAS) is associated with an increased cardiovascular morbidity. In a recent study Garrigue, et al. 2002 first reported a reduction of Apnea/Hypopnea Index (AHI) in dual chamber pacemaker (PM) patients with sleep apnea during dual chamber demand (DDD) overdrive pacing. The aim of our study was the analysis of the amount and duration of apneas and hypopneas in SAS patients during dual chamber or atrial nocturnal overdrive pacing (NOP) compared to spontaneous nocturnal rhythm with backup pacing.
Methods: This single blind, crossover study used DDD or atrial demand PM modes. The control arm PM lower rate (LR) was set to 45 beats/min at night; NOP arm LR was 75 beats/min at night. Daytime LR was 60 beats/min for both arms. Day/night LR switched automatically using the PM sleep function. Subjects remained in each arm for 1 week. A polygraphy recording was conducted for screening and a polysomnography at the end of each week. Subjects with diagnosed SAS, without permanent atrial arrhythmia, and with atrial or dual chamber PM with the sleep function were recruited.
Results: Sixteen subjects, 13 male, age 70±8 yrs (Mean±SD) had a BMI of 30.7±5.9 kg/m2. Indications for PM were sinus arrest in 6, AV block in 8, sinus arrest and AV block in 1, and bradycardic response to atrial fibrillation in 1. No changes were detected in the amount and duration of apneas and hypopneas (AHI, Control 30±17, NOP 29±24; Apnea Duration, Control 21.0±8.6 sec, NOP 18.3±11.4 sec; Hypopnea Duration, Control 21.1±5.6, NOP 17.8±6.9 sec), in minimum oxygen saturation (Control 74±15%, NOP 79±13%) and in sleep structure, Total Sleep Time (Control 325±81 min, NOP 320±103 min) and sleep stages 1, 2, SWS and REM. Mean heart rate was significantly higher during NOP (Control 63±9, NOP 78±5 beats/min, P<0.0001).
Conclusion: Although NOP did not influence sleep and did not reduce the severity of SAS in pacemaker patients, some individual improvements suggest that patient selection may be important.

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Fatigue and Sleepiness Associated With OSAS and UARS

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Introduction: Fatigue is a non-specific symptom that can be associated with physical illness and psychiatric disorders. Mental and physical well-being can be impaired as a result of fatigue. Another disabling symptom, daytime sleepiness, has been associated with Upper Airway Resistance Syndrome (UARS) and Obstructive Sleep Apnea Syndrome (OSAS). UARS can present with tiredness, fatigue, nocturnal disrupted sleep, frank insomnia, and myalgia with tender points, similar to those seen in patients with fibromyalgia and depression. Compared to OSAS, UARS patients have more functional somatic complaints. The objective of this study was to determine whether sleepiness and fatigue complaints differ between the two groups.
Methods: 91 subjects (41 men and 50 women) suspected of having sleep disordered breathing based upon clinical interviews and 22 control subjects without complaints suggestive of sleep disordered breathing or other sleep disorder underwent prospective polysomnographic monitoring. All subjects completed the Epworth Sleepiness Scale (ESS) and 2 validated fatigue scales: Fatigue Severity Scale (FSS) of Krupp et al and The Fatigue Scale (TFS) of Chalder et al. Higher scores for both scales indicate greater fatigue. FSS consists of 9 items rated 1 to 7, and we used the calculated mean scores. TFS is composed of 11 items rated 0 to 3 and Likert scoring (0, 1, 2, 3) was performed for these items. From TFS items, we obtained physical and mental fatigue scores. Objective sleepiness was measured utilizing the Multiple Sleep Latency Test (MSLT), which was administered the day following polysomnography. A urine drug screen was performed on the MSLT day.
Results: The mean age for all the groups was 35.1 ± 10.9 years. 32 subects were diagnosed with mild to moderate obstructive sleep apnea with mean RDI of 11.6 ± 8.6 and mean Pes of -15.1 ± 8. 37 subjects were diagnosed with UARS with mean RDI 2.5 ±1.4 and mean Pes of -11.7 ± 6.1. 22 controls had mean RDI of 1.6 ± 1.4 and Pes of -7.5 ± 2.1. TFS score was 20.4 ± 6.5 in OSAS, 20.3 ± 6.1 in UARS patients, and 19.2 ± 5.5 in the control group. FSS scores were 5.2 ± 1.6, 5 ± 1.5 and 4.6 ± 1.8, respectively. There was no significant difference between groups according to fatigue scores. Correlation tests were performed in each group with the following variables: TFS, FSS, ESS, RDI, Pes, and mean sleep latency. In OSAS patients, TFS and FSS scores correlated with ESS. In the UARS group, TFS correlated with ESS and Pes, while FSS only correlated with ESS; no correlation existed between these variables in the control group. None of the fatigue and sleepiness scales correlated with sleep latency measured by the MSLT in any group. Fatigue scores for the total group did not correlate with gender. But within SDB patients, women had significantly higher FSS scores and TFS physical scores.
Conclusion: Fatigue, a frequent symptom associated with SDB, does

not correlate with MSLT scores. Both fatigue scales are easy to apply and helpful in determining the severity of this symptom. Within the subgroup of SDB subjects, this symptom appears more prominently in women.

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Respiratory Pattern Disturbance Following Pedunculopontine Stimulation: Modulation By Serotonin And Noradrenaline

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Introduction: The pedunculopontine tegmental nucleus (PPT) participates in both behavioral state and respiratory pattern regulation, and PPT stimulation evokes various features of REM sleep including respiratory pattern disturbances. Because the PPT receives noradrenergic and serotonergic afferents, we tested the impact of these REM sleep-regulatory neurotransmitters on respiratory pattern variability caused by glutamatergic stimulation of the PPT.
Methods: Experiments were performed in 11 anesthetized (80 mg/kg ketamine and 5 mg/kg xylazine i.p.) Sprague-Dawley rats. Three-barrel micropipettes were filled with oil red-O dye, 10 mM glutamate and 10 mM serotonin (5-HT) or noradrenaline (NA). The pipette assembly was advanced in 100 mm increments from the dorsal margin of the PPT and each site was pressure injected with 5-10 nl of glutamate until a respiratory disturbance, characterized by at least one apnea (breath time > 2.5 s), was observed. In 8 rats we examined the direct effect of 5-HT (5-10 nl) on respiratory pattern, and the impact of this pretreatment on the respiratory response to glutamate. In a second group (n=3) we tested the effects of NA in the same manner. Respiratory movements were monitored by piezoelectric strain gauge.
Results: Histological analysis verified that all functionally identified sites were within the PPT (7.64 to 8.30 mm from bregma). The characteristic respiratory response to glutamate injection comprised an immediate apnea of 3 to 10 s duration, followed by increased variability of breath time (TT) and tidal amplitude (VT) for 1 to 2 minutes. To quantify these effects we computed the coefficient of variation for TT (CVTT) and VT (CVVT) for 60 s just before and just after each injection. The effects of each drug were tested by ANOVA single factor analysis and paired t-test. In the first group of rats (5-HT rats) CVTT was 0.12 and for CVVT was 0.06. Glutamate injection increased the variability of TT (CVTT=0.89, $p<0.05$) and VT (CVVT=0.15; $p<0.05$). Although 5-HT injection had no independent effect ($p>0.10$), it significantly blunted the TT variability caused by subsequent glutamate injection (CVTT=0.25, p=0.07 vs. initial glutamate response). In the second group of rats (NA rats) baseline variability for TT (0.12) and VT (0.04) increased after glutamate injection (CVTT=0.70, p=0.06; CVVT =0.27, $p<0.01$). NA injections exerted no direct impact on TT variability ($p>0.10$), but potentiated the impact of subsequent glutamate injections: CVTT=0.90, p=0.04 vs. initial glutamate response. Neither 5-HT nor NA affected CVVT at baseline or after glutamate injection ($p>0.10$ for each).
Conclusion: A subpopulation of PPT neurons involved in respiratory pattern regulation can be functionally identified by probing this region with microinjections of glutamate. Injecting identified sites with equimolar concentration of 5-HT or NA produced no direct effects on respiratory pattern. However, pretreatment with 5-HT blunts, whereas pretreatment with NA potentiates, the glutamate-induced respiratory disturbance. These observations suggest that 5-HT and NA play neuromodulatory roles in the PPT and may be important in sleep-related respiratory disturbances.

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C-Reactive Protein In Non-Obese And Obese Obstructive Sleep Apnea Subjects

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Introduction: Elevated C-reactive protein (CRP) is a risk factor for cardiovascular events. Increased CRP levels have been reported in patients with metabolic syndromes (upper body obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol levels, hypertension and abnormal glucose), as well as in patients with obstructive sleep apnea syndromes (OSAS), but most of the affected sleep apnea patients were obese. The role of OSAS vs. obesity in producing elevated CRP levels is unclear. The objective of this study was to prospectively evaluate CRP levels in patients with sleep disordered breathing.
Methods: Serum CRP levels were obtained from 140 subjects (79 OSAS, 24 upper airway resistance syndrome [UARS], and 37 normals) and analyzed using a nephelometric technique. All subjects completed a validated sleep questionnaire, Epworth Sleepiness Scale, and 3 different fatigue scales, followed by clinical evaluation including body mass index (BMI) and hip/waist ratio determinations, neck circumference and cranio-facial measurements, and polysomnographic testing.
Results: Using Tamhane posthoc tests, UARS subjects were younger compared to OSAS and control subjects; OSAS subjects had higher BMI and systolic and diastolic BP recordings than UARS and control subjects; RDI was highest and SaO2 was the lowest in the OSAS subjects, while control subjects had the lowest RDI and highest SaO2 levels. Control subjects had a significantly less negative peak end inspiratory esophageal pressure (Pes) than the OSAS and UARS subjects. The mean CRP level for the entire group was 0.517 ± 0.36 mg/dl; OSAS patients had a mean level of 0.534 ± 0.043 mg/dL, compared to UARS patients, who had a mean level of 0.471 ± 0.35 mg/dL; control subjects had a mean of 0.509 ± 0.10 mg/dL. All measurements were within normal limits and the differences in mean CRP levels were not significant. Nine subjects with sleep-disordered breathing (8 OSAS and 1 UARS) had abnormally elevated (>0.900 mg/dL) CRP levels. Spearman's correlation coefficient analysis yielded significant levels at the 0.05 and 0.01 levels for the parameters of BMI, RDI, maximum Pes value, and lowest SaO2. Stepwise regression analysis using CRP as a dependent variable yielded BMI as the only significant variable in the model ($R2 = 0.180$, beta = 0.435,p = 0.0001). Kruskall-Wallis ANOVA analysis revealed that age and BMI were the 2 significant variables in men ($p = 0.003$ and 0.0001, respectively), while BMI was the only significant variable in women ($p = 0.01$). Women with high CRP levels had significantly higher mean RDI values of 42 ± 40 events/hour and higher maximum mean negative peak Pes values of -32 ±14.7, compared to RDI of 9 ± 15.4 events/hour and Pes values of -11.8 ± 7 in women with normal CRP ($p= 0.006$ and $p = 0.02$, respectively).
Conclusion: In our sample of non-obese subjects with moderately severe obstructive sleep apnea, CRP levels were not significantly different compared to those in control subjects. Abnormal CRP levels were only seen in SDB subjects who were obese. RDI had no impact on serum CRP levels.

Compumedics (TM) loaned the Sierra Sleep Systems for the sleep studies.

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Pulmonary Hypertension, Heart Failure and Sleep Apnea

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Introduction: Previous research has identified risk factors for sleep disordered breathing (SDB) in heart failure (HF) patients, and prior studies have documented that about half of all HF patients have SDB, but most studies have not included an evaluation of pulmonary artery pressures in these patients. The purpose of the study was to determine the frequency of sleep disordered breathing in HF patients with pulmonary hypertension (PH) compared to HF patients with normal pulmonary artery pressures.
Methods: Left ventricular systolic dysfunction was defined as an ejection fraction <45%. Pulmonary hypertension was defined as an estimated pulmonary artery pressure >35 mm Hg. Sleep disordered breathing (SDB) was defined as a respiratory disturbance index > 15. Subjects underwent overnight polysomnography along with questionnaire evaluations of daytime sleepiness and fatigability.
Results: Sixteen subjects completed the protocol, 9 of whom had pulmonary hypertension, and 7 of whom had normal pulmonary artery pressures. There were no differences between the two groups in terms of age, body mass index, ejection fraction, respiratory disturbance index, baseline oxygen saturation, daytime fatigue, and daytime sleepiness. However, eight of 9 (89%) HF patients with PH had OSA, compared with 4 of 7 (57%) subjects without PH had OSA.
Conclusion: In this study, OSA tended to be present more often in HF subjects with PH than in HF subjects with normal pulmonary artery pressures.

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Cognitive Deficits In Obstructive Sleep Apnea Patients Are Correlated With Nocturnal Hypoxemia Rather Than With Sleep Fragmentation

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Introduction: Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of upper airway obstruction during sleep, which are associated with intermittent nocturnal oxyhemoglobin desaturations and sleep fragmentation. OSAS patients present with impairments in general intellectual abilities including verbal, executive, psychomotor functions, attention and memory. Multiple studies suggest that cognitive dysfunction in patients with OSAS may be the result of chronic intermittent oxyhemoglobin desaturation, although the relative importance of sleep fragmentation versus brain hypoxemia is still debated.
Methods: Overnight polysomnography (PSG) was performed in 39 mild to severe OSAS patients (mean age=39, SD=13.1, mean BMI= 28, SD=7.6). During the day following PSG, a multiple sleep latency test (MSLT) was performed followed by evaluation of cognitive functioning. Cognitive tasks included: serial subtraction (working memory), grammatical transformation (processing speed), tangled line (visual scan), and Macworth clock (vigilance). In addition, subjective sleepiness was assessed using the Stanford Sleepiness Scale (SSS) and a visual analogue scale (VAS). Correlations between subjective measurements of sleepiness, MSLT scores, cognitive functioning, PSG parameters (e.g. respiratory disturbance index (RDI), minimal oxygen saturation, number of arousals and awakenings), and nocturnal oxygen saturation prior to sleep (wake saturation) were calculated. Cognitive tasks score were transformed to Z-scores and two new variables were created reflecting performance speed and performance accuracy over different tasks.
Results: RDI was correlated with performance speed ($r=.44$, $p<0.01$) grammatical transformation ($r=.4$, $p<0.05$) and visual scanning tasks ($r=.42$, $p<0.01$). Minimal nocturnal oxygen saturation was correlated with performance accuracy ($r=-.42$, $p<0.01$) and serial subtraction task ($r=-.36$, $p<0.05$). Wake oxygen saturation was correlated with performance speed ($r=-.48$, $p<0.01$), grammatical transformation ($r=-.56$, $p<0.01$) and visual scan tasks ($r=-.47$, $p<0.01$). Number of arousals and awakenings were not correlated with performance on any of the cognitive tasks. MSLT was neither significantly correlated with cognitive performance nor with subjective sleepiness.
Conclusion: Both speed and accuracy on cognitive tasks performance are related to measurements of nocturnal oxygen desaturation (RDI, minimal oxygen saturation), rather than measurements of sleep fragmentation (number of arousals or awakenings). Wake oxygen saturation, as measured prior to sleep, may also be an important factor related to cognitive performance. Objective sleepiness, as measured by MSLT, did not correlate with either cognitive performance or subjective measurements of sleepiness. In conclusion, cognitive deficits in patients with OSAS may be the result of oxygen desaturations during sleep and baseline saturation (wake), rather than the result of sleep fragmentation or sleepiness per se. This study may support the notion that chronic oxygen desaturations may affect brain functioning. Further research using advanced brain imaging techniques is required in order to shed some more light on possible mechanisms.

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Changes In EEG And EMG Power Spectra Associated With Respiratory Disturbance Following Stimulation Of Pedunculopontine Tegmentum

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Introduction: The pedunculopontine tegmental nucleus (PPT) plays an important role in regulating sleep and wakefulness, and this role is reflected in characteristic electroencephalographic activity such as PGO waves, hippocampus theta rhythm and cortical activation. We recently demonstrated significant modulation of respiratory pattern by PPT neurons, and this study characterized the correlation of EEG and EMG changes with respiratory disturbance induced by glutamatergic stimulation of PPT.
Methods: In 7 anesthetized (ketamine: 80mg/kg; xylazine: 5 mg/kg i.p.) Sprague-Dawley rats, we recorded contralateral pontine and bilateral cortical and hippocampal EEG, as well as genioglossus EMG. Respiratory movements were monitored by piezoelectric strain gauge. Three-barrel micropipettes were filled with saline, glutamate (10 mM), and oil red-O dye. Glutamate was injected (5 to 10 nl) at 100 mm intervals through PPT. Red dye was injected to aid histological verifications of injection sites producing respiratory disturbances.
Results: At effective PPT sites, glutamate induced severe respiratory instability characterized by alternating periods of tachypnea and bradypnea and/or apnea. The typical response required 30 to 180 s to become fully developed and lasted more than one hour. To quantify these changes in respiratory pattern stability, we computed coefficients of variation for breath duration (CVTT) and tidal amplitude (CVVT) in 30 s epochs during baseline, for one epoch preceding each injection and for two minutes following each injection. To quantify EEG synchronization/activation and EMG activation we computed EEG and EMG power,

respectively, on 10 s epochs at baseline as well as before and after each injection. Time-dependent changes after glutamate injection were tested using repeated measures ANOVA and paired t-tests. The initial response comprised an immediate increase in contralateral cortical EEG power lasting 20 seconds ($p<0.05$) followed by increased EMG power 10 to 20 s after glutamate injection ($p<0.05$). Increased respiratory variability was delayed until 30 s after injection, and subsequently lasted throughout the 2-minute response interval ($p<0.01$). Coincident with the onset of respiratory variability, contralateral pontine activation was evidenced as a transient decrease of EEG power 30 to 40 s post-injection ($p<0.01$) and ipsilateral cortical activation was demonstrated by decreased EEG power that persisted throughout the two-minute response interval ($p< 0.01$). Bilateral hippocampus EEG power tended to decrease during 20-30 s post-injection ($p=0.07$).

Conclusion: PPT stimulation by nanoliter volumes of glutamate in ketamine/xylazine anesthetized rats produces complex responses including at least: site-specific EEG changes, upper airway motor alterations, and respiratory dysrhythmia. In particular, the electrocortical response was striking: contralateral sychronization followed by ipsilateral activation. The coincident time courses for the respiratory disturbance and the ipsilateral cortical response supports the possibility that cortical activation may be permissive of, or even causal to the observed respiratory dysrhymia.

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Slope Of Flow Limited Breaths Rather Than Flow Limitation Is The Cause Of Arousal

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Introduction: Since the introduction of nasal-pressure cannula (NPC), there has been wide spread usage of this technology. Likewise, significant literature supporting the superiority of the NPC as compared to nasal thermistor. Most of the articles describe the variety of the inspiratory contour to determine flow limitation, but none have evaluted the enitre shape of the NPC signal, especially the slope of the flow limited breaths. The objective of this study is to determine whether or not the flow limited breaths, rather than the slope of the flow limitation, is the cause of arousal.

Methods: We evaluated the entire shape and slope of flow limited breaths by NPC and compared to only the contour of the inspiratory plateau prior to arousals. The PSGs of 280 patients, ages 12-70, 180 females and 100 males referred to the sleep laboratory for obstructive sleep apnea, were evaluated. All patients were monitored with NPC including the square root. The shape of the signal was divided into 6 different segments, including the starting point of inspiration, peak inspiration, plateau, expiratory deflection, expiration, and pause. The slope was measured from exponent of infinity to the last breath prior to arousal.

Results: In our study, we determined that regardless of the extent of flow limitation and the contour of the inspriatory plateau, as long as the slope had not changed, arousals did not occur. Arousals were only seen when the slope of the flow limited breaths started to rise. Prior to the arousals, several changes occurred in the NP signal prior to rescue breaths indicative of arousals, and these include: Onset of inspriation gradually started to rise from the baseline, rise time lengthened, slope of the rise time became steeper, and inspiratory portion flattened. The end of the inspiratory plateau may or may not be associated with expiratory muscle contraction. Just before the rescue breaths, exhalation time lengthened the most, and most importantly, the slope of the flow limtied breaths gradually increased prior to arousals.

Conclusion: We demonstrated that as long as the slope of the flow limited breath does not change, arousals do not occur, regardless of the contour of the inspiratory portion of the nasal pressure signal. It appears from the slope of the flow limited breaths, auto PEEP started to develop and gradually worsen prior to normalization of breaths. CPAP may in part work to overcome the auto PEEP to alleviate obstructive respiratory events.

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CPAP Significantly Increases EKG Premature Ventricular Contractions At Lower Pressures

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Introduction: While there have been rare reports of CPAP complications such as conjunctivitis, pneumocephalus, and epistaxis, no dangerous complication has been commonly reported. Some case reports, however, indicate cardiac arrhythmias emerging with CPAP treatment. We used retrospective hospital sleep clinic records to examine this issue.

Methods: Over a 2-year period, all 1251 subjects undergoing routine clinical polysomnography were screened and included if one or more PVCs were seen on either baseline or CPAP night. PVCs were identified manually and coded as to: sleep / wake, baseline night / CPAP night, sleep stage, CPAP pressure, and body position. Where possible, the index per minute (PVCi) was calculated. The difference in the total number of PVCs on the baseline vs. CPAP night was calculated, resulting in a new variable CHANGE, with 3 levels - Reducers (32 cases), NoChangers (60 cases), and Increasers (34 cases). Any drugs taken were coded present / absent in 5 categories: benzodiazepines (BZD), opiates, antidepressants (AD), anti-hypertensives (A-HTN, including calcium channel blockers, ACE inhibitors, beta-blockers), and anti-arrhythmia agents (A-Arr). These variables, plus the Beck Depression Inventory, Epworth Sleepiness Scale, body mass index, and age were used in a logistic regression to predict the dependent variable CHANGE. To assess the effect of different CPAP pressures on PVCs, a MANCOVA design was used: repeated measures of PVCi (baseline night vs. 10 levels of CPAP pressures from 3 - 12 cm of water, PRESSURE) x SEX x CHANGE. CPAP night PVCi was used as a covariate to reduce intersubject variance. Contrasts between baseline PVCi and PVCi at all CPAP pressures were calculated.

Results: In all, 493 / 1251 patients (39%) received CPAP, and of these, 31 women and 94 men (n=126, or 25%) demonstrated PVCs. A chi-squared test of SEX x CHANGE was not significant. Logistic regression showed that the presence of opiates ($p < 0.006$) and BZDs ($p < 0.036$) were significantly associated with higher PVCi on the CPAP night, whereas there was a significant protective effect of A-Arr medications ($p < 0.035$). None of the other variables reached significance. The MANCOVA was globally significant ($p < 0.05$), as was PRESSURE within-subjects ($p < 0.004$), and PRESSURE x CHANGE ($p < 0.0001$), but not SEX. Compared to baseline PVCi, there was significantly greater PVCi at CPAP pressures of 3, 4, and 8-12 cm. ($p < 0.02$ - 0.007). Surprisingly, many Increasers had few PVCs on the baseline night, but increased to quite high PVCi during CPAP at 3 and 4 cm pressure, only to decline to near baseline at higher pressures.

Conclusion: This is the first large systematic report of CPAP increasing PVCs in some patients. The effect appears greatest when CPAP is first applied at low pressures to patients with relatively few PVCs on their baseline study, possibly suggesting stress or fear reactions, but a respiratory mechanism cannot be ruled out. It is more likely in those taking BZD and opiate medications, and less likely with anti-arrhythmia drugs.

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Defining Parameters Of The Diagnostic Portion Of A Split Night Protocol

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Introduction: Medicare guidelines state two full hours of total sleep time (TST) must be recorded, and that a respiratory disturbance index (RDI) of 15 must be demonstrated without extrapolation. The split night CPAP titration protocol has been used in order to reduce the time from diagnosis to treatment, and to realize possible cost savings to third party reimbursers. The lack of a standardized split night protocol has been widely noted. Studies have demonstrated an RDI of < 20 and an ensuing titration time of < 180 minutes, yield less than optimal results when utilizing a split night protocol. Medicare guidelines suggest that once 120 minutes of sleep is obtained and an RDI of 15 has been reached, the patient could then benefit from CPAP intervention. The suggestion is therefore made that the Medicare guidelines could be used to define the parameters of the diagnostic portion of a split night protocol.
Methods: Archival data was collected from 1388 PSGs performed over a 12-month period. Of those, 710 studies were found that required the use of CPAP. Data was then collated and 456 split nights (SN) were compared to 254 two night (TN) protocol studies. Severity, RDI, & TST data were then assessed. A split night study was defined as successful if no need for further titration studies were required.
Results: 305 of the 456 SN studies were considered successful, while 151 required an additional titration study night. 53% of failed split nights had a diagnostic (DX) portion RDI of <20, 15% had an RDI of >20 & < 40, and 32% had an RDI of >40. 17% had a DX TST of <120 minutes, another 17% had a DX TST of >120 & <180 minutes, but only 5.7% had a DX TST of >180 minutes & <240 minutes. 60% were >240 minutes, reflecting insufficient time remaining for adequate titration.
Conclusion: In the absence of significant health related severity (i.e. cardiac arrhythmias or significant hypoxia), and with an RDI of < 20 to 40 coupled with less than 3 to 4 hours of sleep time, a split night should be converted to a two night protocol. Using Medicare guidelines (to start CPAP with an RDI of 15 after 120 minutes of sleep time) to define the split night diagnostic parameters may not promise a successful CPAP titration, and additional studies would then be required to successfully titrate the patient, countering the advantage of performing a split night protocol in the first place. The ensuing patient compliance to treatment might also be impaired, with a negative impression of treatment, by the need for a repeat study.

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Nuclear Factor Kappa B in Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) may lead to cardiovascular disease by increasing atherogenesis. However, underlying mechanisms remain unknown. Nuclear Factor kappa B (NF-kB) is an important pro-inflammatory transcription factor known to play a significant role in the pathogensis of atherosclerosis. We therefore investigated NF-kB activation in normal subjects and in patients with OSA.
Methods: Seven OSA patients, apnea hypopnea index (AHI) >40/hr, and 9 normal subjects, AHI =/<5/hr (control group), determined by overnight polysomnography, were included. Morning fasting venous blood samples were obtained after nocturnal polysomnogrpahy. Peripheral neutrophils were isolated and nuclear protein was extracted. NF-kB activity was measured by electrophoretic mobility shift assay using P32 labeled oligonucleotides containing the NF-kB binding site. Plasma soluble E-Selectin and vascular cell adhesion molecule 1 (sVCAM-1) were also measured using ELISA.
Results: The age, BMI and AHI of control and patient groups was 35.8+/-7.7 vs. 42.7+/-6.5 yrs, 23.5+/-3.4 vs. 41.2+/-8.7 kg/m2; 4.05+/-1.6 vs. 84.9+/-38.5 /hr respectively. Minimal NF-kB activity was detected in nuclear protein from neutrophils of control subjects. In contrast, markedly greater NF-kB activity was observed in OSA patients. We quantified band intensity of NF-kB binding activity using densitometry (arbitrary units). The optical density units for the control vs. OSA group is 436 +/- 143 vs. 3162 +/- 590, p<.0001. We determined the consequences of NF-kB activation by assaying the products of two important NF-kB regulated genes, E-selectin and VCAM-1. Plasma sE-selectin levels in control and OSA groups are 26.6 +/- 4.5 vs. 56.9 +/- 7.5, ng/ml, p<0.005; plasma sVCAM-1 levels are 272 +/- 28 vs. 532.1 +/- 113 ng/ml, p<0.005.
Conclusion: OSA patients have increased NF-kB activity in circulating neutrophils and increased expresion of NF-kB dependent gene products suggesting that activation of NF-kB pathways may contribute to atherogenesis and cardiovascular dysfunction in OSA.

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The Value of the Epworth Sleepiness Score as a Screening Tool Either Alone or in Combination with Obesity and Snoring

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Introduction: Excessive daytime somnolence (EDS) is often a presenting symptom for sleep-disordered breathing (SDB). Although SDB affects an estimated 2-4% of the adult population, it is under-recognized and its true incidence is not known. Under-diagnosis has been attributed to the lack of good screening tests. The Epworth Sleepiness Scale (ESS) is a self-administered eight-item questionnaire that has been validated as a screening test for SDB. However, its validity has recently been challenged. Other criteria, such as BMI, presence of habitual snoring, neck circumference, hypertension, and bed partner's report of nocturnal gasping/choking have been suggested to be reliable clinical predictors of SDB.
Methods: This study was conducted to assess the sensitivity and positive predictive values of an ESS score ≥ 9 OR the presence of BMI ≥ 25 and snoring for SDB in patients presenting to the pulmonary practice at Mount Sinai Medical Center. Patients were given a self-administered questionnaire that included the ESS, height, weight and the presence or absence of snoring. Those with an ESS score ≥ 9 OR those with a BMI ≥ 25 and snoring were referred for nocturnal polysomnography (NPSG).
Results: Forty-three patients with a positive screening questionnaire underwent a NPSG from July through October 2003. Of these, 39 had an apnea/hypopnea index (AHI) greater than 5, indicating the presence of the obstructive sleep apnea hypopnea syndrome (OSAHS). The mean AHI for patients with OSAHS was 27.5 (± 8.22). Of those patients with OSAHS, 27 had an ESS ≥ 9, yielding a sensitivity of 0.69 (95% CI: 0.52-0.82). The positive predictive value for an ESS ≥ 9 was 0.87 (95% CI: 0.70-0.96). There was no significant difference in the age and sex distribution of patients with an ESS greater than or less than 9. The sensitivity and positive predictive value of the combination of snoring and a BMI ≥ 25 was 0.94 and 0.92 (95% CI: 0.82-0.99 and 0.79-0.98) respectively. For a BMI greater than 30, sensitivity and specificity increased to 1.0 (95% CI: 0.88-1.0). There was a direct relationship between BMI and AHI (r= 0.44, p= 0.003). There was no relationship between ESS score and BMI.
Conclusion: These preliminary data indicate that the sensitivity and positive predictive value of the ESS can be improved by also evaluating

snoring patients with an increased BMI.

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Resolution Of Obstructive Sleep Apnea After Stabilization Of Critical Illness

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Introduction: Obstructive sleep apnea (OSA) has been associated with critical illness. Our microneurography studies suggest that the autonomic effects of OSA could put such patients at significant additional health risks. As such, determining if certain medical intensive care unit (MICU) sub-populations are at risk for acute/chronic OSA may be of great value in justifying aggressive polysomnography (PSG) in the MICU setting, specific therapeutic interventions, and follow-up PSGs.
Methods: An institutional review board on humans studies approved this research. Over 50-days all patients admitted to the MICU, 18 years and older, were offered enrollment (128 subjects). Initial PSGs would be performed in the MICU, followed by studies when clinically stable. Thirty-five percent of eligible patients (44) participated. Significant OSA was determined as an apnea-hypopnea index (AHI) of 5 or greater.
Results: Resolution of significant OSA was appreciated in 3 of the 11 patients diagnosed with OSA for whom a repeat PSG was possible. In patients with persistent OSA, CPAP was successful in 6, tracheostomy was required in 1, and treatment was refused by 1. Resolution of OSA was seen in a 30-year old woman with methadone overdose. Her initial study revealed, with head-of-bed (HOB) elevated 30 degrees, an AHI of 43, an SaO2 low of 85%. Her follow-up PSG after 60-days, with HOB flat, showed an AHI of 0.2. She lost 6 kilograms (kg). In the MICU she routinely received neurontin, quetiapine, and lansoprozole, and upon follow-up medications included melatonin, acetaminophen, and ibuprofen. The second patient with OSA resolution was a 48-year old woman admitted with pancreatitis. Her first study, while receiving 2 liters of O2, with HOB elevated 45 degrees, revealed an AHI of 40, an SaO2 low of 90% (with a baseline of 98%). A follow-up PSG in 67 days, without supplemental O2, with HOB elevated 30 degrees, showed an AHI of 4.4. She lost 14 kg. Regularly scheduled MICU medications included hydrocortisone, famotidine, pantoprazole, nalbuphine, and insulin. On follow-up she was taking amitriptyline, folate, levothyroxine, prednisone, diazepam, hydromorphone hydrochloride, and lansoprazole. The third subject with resolution of OSA was a 37-year old woman admitted for cystic fibrosis exacerbation. Her initial study, while receiving 1 1/2 liters of O2, with HOB elevated 30 degrees, revealed an AHI of 26 and an SaO2 low of 82%. The follow-up PSG after 105 days showed an AHI of 2.8. Her weight did not change. In the MICU she received lansoprazole, tobramycin, and dornasl alfa, albuterol, fluticasone-salmeterol and ipratropium inhalations, insulin, alendronate, levofloxacin, pancrealipase, whereas on follow-up she regularly used only insulin, lansoprozole, and inhalers. Of these 3-patients, the mean AHI improved from 36 to 2, and the SaO2 low values improved from 86% to 93%. In addition, there was a mean weight loss of 7 kg between studies. Of the subjects with persistent OSA the primary admitting diagnoses included chronic obstructive pulmonary disease, diabetic hyperglycemia, bronchiolysis obliterans organizing pneumonia, acute pancreatitis, diabetic ketoacidosis, cerebral aneurysm, congestive heart failure, and alcoholic liver disease.
Conclusion: The treatment of our critically ill patients with drug overdose, pancreatitis, and cystic fibrosis, was associated with a resolution of significant OSA. The explanation may be due to a combination of elements that may effect central respiratory centers. This includes not only the primary diagnosis, but medications, body weight, and body position during the PSG study. We hope to use this research to help rationalize larger, more detailed populations studies to further delineate significant clinical associates of OSA in the critically ill. This information would greatly assist in justifying the aggressive use of PSG in the MICU setting.

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Insulin Resistance and Sleep Apnea in Medical Check-up Subjects

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Introduction: Sleep apnea is associated with dyslipidemia and insulin resistance, independently of obesity. While there have been some reports documenting the association, they are mainly based on data from sleep laboratories. We analyzed data from subjects who had medical check-ups and who were basically asymptomatic.
Methods: In consecutive subjects who took a 2-day medical check-up at our facility from April 2002 to July 2003, fasting serum lipids, uric acid (UA), glucose, and insulin were obtained the morning after undergoing overnight pulse oximetry. Insulin resistance (IR) was assessed using the homeostasis model assessment (HOMA) and defined as HOMA≥2 being IR(+). The subjects were divided into IR(+)[HOMA≥2] and IR(-)[HOMA < 2] groups. Oxygen desaturation index for 3% or more dips per hour (ODI3) and the lowest value of saturation (low-SpO2) were used to evaluate the pulse oximetry records. The analyses were done in two steps: [Analysis 1] sex, age, ODI3, body mass index (BMI), lipids, low-SpO2, and mean blood pressure (MBP) were compared between IR(-) and IR(+) groups; [Analysis 2] a nominal logistic regression analysis was done with IR(-) or IR(+) selected as response and with the variables that yielded statistically significant difference in Analysis 1 and age selected as factors. Data from 602 subjects (mean age 50.4, 470 male, 132 female) were used for the analyses.
Results: Analysis 1: The results were shown as Term (Unit): [IR(-) mean ± SD vs. IR(+) mean ± SD; p-value]. Age(years):[50.0 ± 8.2 vs. 51.8 ± 9.0; NS] Sex (Male/Female):[377/120 vs. 93/12; 0.0042] ODI3(events/hour):[4.07 ± 5.2 vs. 9.02 ± 7.8; <0.0001] BMI(kg/m2):[22.8 ± 2.49 vs. 26.4 ± 3.2; <0.0001] UA(mg/dl) :[5.51 ± 1.3 vs. 6.05 ± 1.4; 0.0005] Triglyceride (TG) (mg/dl) :[111.0 ± 72.0 vs. 169 ± 96.7; <0.0001] Total Cholesterol(TC)(mg/dl) :[208.9 ± 33.0 vs. 212.5 ± 40.1; 0.6651] Low-Density Lipoprotein Cholesterol (LDL-C)(mg/dl) :[128.3 ± 31.2 vs. 131.6 ± 37.3; 0.7071] High-Density Lipoprotein Cholesterol (HDL-C)(mg/dl) :[58.3 ± 16.4 vs. 47.1 ± 12.5; <0.0001] MBP(Torr):[87.0 ± 11.1 vs. 92.4 ± 11.4; <0.0001] low-SpO2(%) :[87.0 ± 10.3 vs. 84.5 ± 8.5; <0.0001] Analysis 1 showed that Male/Female ratio, ODI3, BMI, UA, TG, and MBP were significantly higher in IR(+) group than in IR(-) group and that HDL-C and low-SpO2 were significantly lower in IR(+) group than in IR(-) group. These "significant" variables (sex, ODI3, BMI, UA, TG, MBP, HDL-C, and low-SpO2) and age were selected as factors in Analysis 2. Analysis 2: The results of effects likelihood ratio tests were shown as Source:[DF; Likelihood Ratio Chi-Square; p-value]. BMI:[1; 53.0005381; 0.0000] HDL-C:[1; 6.95166971; 0.0084] TG:[1; 4.76157749; 0.0291] ODI3:[1; 3.96550706; 0.0464] Age:[4; 8.77690169; 0.0669] MBP:[1; 0.42519031; 0.5144] Sex:[1; 0.00039633; 0.9841] UA:[1; 0.0001553; 0.9901].
Conclusion: The data from our medical check-up setting also suggested that sleep apnea is associated with dyslipidemia and insulin resistance, independently of obesity.

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Femtomole Injections Of Glutamate Into The Intertrigeminal Region Alter Respiratory Pattern

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Introduction: From our previously reported data, it appears that a physiological role of the pontine intertrigeminal region (ITR) is to attenuate both reflex and sleep-related spontaneous apneas. In the view of these studies, we conducted the present experiment to determine the dose-response characteristics for changes in respiratory motoneuronal activity induced by injecting nanoliter volumes of L-glutamate (Glu) into the ITR.
Methods: Respiration was recorded by a thoracic piezoelectric crystal in 41 ketamine-anesthetized, spontaneously breathing Sprague-Dawley rats. Multibarrel micropipettes were used for pressure-injection of Glu, PBS (vehicle) or a dye (to mark injection sites) into the ITR, unilaterally. Injection volumes were measured directly by monitoring movement of the fluid meniscus in the pipette barrel. Ten Glu concentrations were tested: 10-2, 5 x 10-3, 10-3, 10-4, 10-5, 10-6, 10-7, 10-8, 10-9 and 0 (PBS) molar. Three Glu concentrations were tested per animal. In each experiment, either 10-2M or 10-3M Glu was used for initial injections to identify an apnea-genic site, at which 2 lower Glu concentrations and the dye were then sequentially injected. Each rat was transcardially perfused under anesthesia and the brain was removed for histological determination of the injection sites.
Results: For each glutamate concentration in each animal, we measured the Threshold Volume (TV) as the lowest injection volume able to evoke an apnea, defined as cessation of respiration for at least 2.5 seconds. Threshold volume (5-20 nl) injections of Glu at all concentrations elicited highly stereotyped apneic responses ($p > 0.1$ for effect of concentration on apnea duration by ANOVA). For this reason, the relationship between Threshold Volume and concentration defines the dose-response characteristic for glutamate-induced apnea of fixed duration. The change in TV as a function of Glu concentration comprised 3 distinct regions: 1) for concentrations ≥ 10-5M, TV was independent of concentration and equal to 7.54 ± 0.38 nl; 2) between 10-5M and10-7M TV increased almost linearly to 16.82 ± 1.4 nl ($p < 0.004$ by t-test); for concentrations of 10-8 M and 10-9M a discontinuity occurred and TV was again lower (14.6 ± 1.23, $p = 0.03$ vs TV for 10-7M) and equivalent for the two concentrations ($p > 0.4$). Further, only the two lowest concentrations produced sustained changes in respiratory pattern (lasting at least 30 s) after the initial apnea. Microinjections of PBS of up to 35nl were unable to evoke apnea.
Conclusion: The study demonstrates that reproducible alterations of respiratory motoneuronal activity can be evoked by injecting as little as 1.35 x 10-17 moles of Glu into the rat brain-stem. It appears from the present experiment that the most important factor governing apnea induction by glutamate injections to ITR is the number of neurons affected. Even very high concentrations of Glu cannot evoke apnea at less than 5 nl injection volume. Even when TV increases at lower concentrations the increase is not in proportion to the decrease of concentration. Finally, the discontinuous dose-response suggests that glutamate may impact respiratory pattern by multiple synaptic mechanisms within the ITR.

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Familial Comparison of Adipose Tissue in the Abdomen and Head/Neck

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Introduction: Obesity is a known risk factor for obstructive sleep apnea. In order to study adipose tissue distributions we quantified the amount of visceral and subcutaneous adipose tissue in the head/neck and abdomen with magnetic resonance imaging in probands with sleep apnea, siblings of the probands, controls and their siblings. We hypothesized that the apneic siblings would have intermediate levels of adipose tissue compared to the apneics and controls.
Methods: Visceral and subcutaneous fat in the head/neck region surrounding the upper airway and abdominal region was quantified on axial T-1 magnetic resonance images using a validated computer software program (Volumetric Image Display Analysis {VIDA}). The head/neck region was defined from the top of the soft palate to the appearance of the epiglottis and the abdominal region was defined from the end of the xiphoid process to the appearance of the iliac crest. T-tests were utilized to determine significant differences ($p < 0.05$) between the volume of visceral and subcutaneous fat in the abdominal and head/neck regions.
Results: We studied 23 probands (age: 44.5 ± 9.8 yrs, BMI: 35.6 ± 8.2 kg/m2, RDI: 44.5 ± 28.9 events/hr), 25 proband-siblings (age: 43.28± 11.19 yrs, BMI: 29.11 ± 5.92 kg/m2, RDI: 10.43 ± 13.21 events/hr), 29 neighborhood controls (age: 43.45 ± 9.9 yrs, BMI: 26.35 ± 4.73 kg/m2, RDI: 2.01 ± 1.61 events/hr), and 24 control-siblings (age: 37.63 ± 9.21 yrs, BMI: 25.54 ± 4.08 kg/m2, RDI: 5.07 ± 4.40 events/hr). We found in the abdominal region the average volume of visceral fat (2,346,945 ± 997,002 mm3) was significantly greater ($p < 0.0001$) in probands compared to controls (1,048,953 ± 750,885 mm3). The percent difference in visceral abdominal fat between the probands and the controls was 55.3%. The average volume of subcutaneous fat (5,769,640 ± 2,659,706 mm3) in the abdominal region was significantly greater ($p < 0.0001$) in probands compared to controls (2,688,739 ± 1,888,453 mm3). The percent difference in subcutaneous abdominal fat between the probands and the controls was 53.4%. In the head/neck region the average volume of visceral fat (178,873 ± 49,168 mm3) was significantly greater ($p < 0.0001$) in probands compared to controls (121,272 ± 36,861 mm3). The percent difference in visceral upper airway fat between the probands and the controls was 32.2%. The average volume of subcutaneous fat (274,363 ± 99,984 mm3) in the head/neck region was significantly greater ($p < 0.0001$) in probands compared to controls (122,549 ± 45,641 mm3). The percent difference in subcutaneous fat between the probands and the controls was 55.3%. The ratio of visceral fat in the abdominal region to visceral fat in the head/neck was significantly greater ($p = 0.0015$) in probands (13.31 ± 4.99) compared to controls (8.47 ± 6.00). The ratio of subcutaneous fat in the abdominal region to subcutaneous fat in the head/neck was not significantly different ($p = 0.2804$) in probands (21.39 ± 9.34) compared to controls (21.74 ± 10.46). This suggests that there is a differental increase in visceral fat comparing the abdomen to the head/neck in apneics compared to normals. The average volumes and ratios of visceral and subcutaneous fat in both regions in the proband-siblings were intermediate between the probands and the controls. There were no differences in the volumes of visceral or subcutaneous fat between the controls and the control-siblings in the abdomen or head/neck.
Conclusion: Patients with sleep apnea have more visceral and subcutaneous fat than controls in the abdomen and surrounding the upper airway. Siblings of apneics have intermediate levels of adipose tissue. The significant difference found in visceral fat when comparing apneics to controls in the abdominal and head/neck region and the equivalent pro-

portionality found in the same comparison of subcutaneous fat reveals that an increase in visceral fat volume may be an important risk factor for sleep apnea.

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Susceptibility To Chronic Intermittent Hypoxia (IH)-Induced Spatial Learning Deficits Is Enhanced Following High Fat/Refined Carbohydrate Diet In The Rat

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Introduction: Exposure to IH, such as occurs in sleep-disordered breathing (SDB), is associated with substantial cognitive impairments and increased neuronal cell loss in brain regions underlying learning and memory in rats. High fat/refined carbohydrate (HF/RC) diets have been associated with cognitive impairments, oxidant stress, and increased vulnerability to neuronal injury.
Methods: Sprague-Dawley male rats were fed on either a HF/RC (n=18) or low fat/complex carbohydrate diet (CO; n=18) starting on post-natal day (PN) 30 and continuing throughout the duration of the experiment. Starting at PN 120, animals were exposed to intermittent hypoxia (IH) consisting of 90 sec alternations of 10% O2 and 21% O2, or room air (RA) for 7 days (12 hours/day during light phase). Behavioral testing consisted of a standard place-training reference memory task in the water maze. Rats were trained to locate a hidden, submerged platform using only distal, spatial cues. On each trial, the rat was placed into the pool from quasirandom start points and allowed a maximum of 90 seconds to escape to the platform, where it was allowed to remain for 15 seconds. Training consisted of one daily 4-trial training session for 4 days. The position of the platform remained constant across trials. To assess performance during place training, mean escape latencies, swim distances, and swim speeds were analyzed by a two-way (hypoxic condition x diet) repeated measures analysis of variance. An additional probe trial was conducted 24 hours after completion of training to assess spatial bias. A p value <0.05 was considered statistically significant.
Results: ANOVA revealed a significant effect of both HF/RC and IH on spatial learning on days 2 and 3 of testing ($p<.03$ for both latency and pathlength, respectively). However, post-hoc analyses revealed that only HF/RC-IH animals failed to reach the level of performance of RA-CO by the end of the training sessions (day 4; $p<.01$ vs. RA-CO). No significant differences were found between groups in regards to swim speeds or the latency and pathlength to locate a cued platform, indicating that group differences were not due to sensorimotor impairments.
Conclusion: Dietary alterations that enhance oxidative stress such as HF/RC are associated with increased susceptibility to intermittent-hypoxia-induced spatial task deficits. These findings may have important implications for interventional strategies targeting nutritional modifications in patients with SDB.

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Increased Vulnerability To Chronic Intermittent Hypoxia (CIH)-Induced Spatial Learning Deficits In Apolipoprotein E-Deficient Mice

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Introduction: Exposure to CIH, such as occurs in Obstructive Sleep Apnea (OSA), is associated with oxidative stress, cognitive impairments, and increased neuronal apoptosis in brain regions involved in learning and memory in rodents. Apolipoprotein E (apoE) has been implicated in neurodegenerative disorders, and in vitro studies suggest that one of the functions of apoE may be to confer protection from oxidant stress-induced neuronal cell loss. Therefore, we hypothesized that apoE-deficient mice would display increased cognitive impairments following CIH exposures.
Methods: 24 young adult male mice (apoE-/-; 25 g) and 24 wild-type littermates (C57/BL/6; 25g) were exposed to 14 days of normoxia (RA, n=12 per group) or CIH (n=12 per group). Behavioral testing consisted of a standard place-training reference memory task in the water maze. Mice were trained to locate a hidden, submerged platform using only distal, spatial cues. On each trial, mice were placed into the pool from quasirandom start points and allowed a maximum of 90 seconds to escape to the platform, where it was allowed to remain for 15 seconds. Training consisted of one daily 3-trial training session for 6 days. The position of the platform remained constant across trials. To assess performance during place training, mean escape latencies, swim distances, and swim speeds were analyzed by a two-way (hypoxic condition x genotype) repeated measures analysis of variance. An additional probe trial was conducted 24 hours after completion of training to assess spatial bias. A p value <0.05 was considered statistically significant.
Results: Both wild-type and apoE-/- mice exposed to IH were found to require significantly longer times (latency) and distances (pathlength) to locate the hidden platform ($p<.03$ for both latency and pathlength), compared to wild-type and apoE-/- mice exposed to RA. However, post-hoc analyses revealed that only apoE-/- mice were impaired on the final two days of training. Additionally, apoE-/- were impaired with respect to all other groups on measures of spatial bias conducted 24 hours after completion of training ($p<.05$). No significant differences were found between groups in regards to swim speeds or on the latency and pathlength to locate a cued platform, indicating that group differences were not due to sensorimotor impairments.
Conclusion: Apolipoprotein E-deficient mice display enhanced behavioral sensitivity to CIH exposures, and thus provide a useful model for investigating the role of this lipoprotein in response to CIH-induced neuronal injury. We speculate that the increased CIH vulnerability of apoE deficient mice may be due to enhancement of oxidative stress, although additional neurodegenerative mechanisms may also be involved.

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Hypertension Prevalence Among Patients With OSAS At The Sleep Diagnostics Center In Budapest

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Introduction: In 1996-97, an epidemiological survey was conducted on 3,500 males aged 40-60 years, who were registered either with 9 family practices in Budapest or the polyclinic in the town of Szazhalombatta. The survey was implemented in strict compliance with the requirements of the Diagnostic and Treatment Protocol of Obstructive Sleep Apnea Syndrome. Main features of the study: 1. Criterion: snoring and/or daytime sleepiness. 2. Number of persons surveyed: N=3,500. 3. Sex: male 4. Age: 40-60 years. 5. Condition confirmed: 1,356. 6. Mild and severe OSAS was found in 10.01% of the sample. 7. From this group, 63.7% required CPAP as therapeutic tool.
Methods: During the 8 years of operation of the Sleep Diagnostics Center, pre-screenings by questionnaire and pulsoxymetric basic screen-

ings were carried out in 15,218 cases; OSAS was confirmed in 14,809 cases. Based on subsequent cardiorespiratory polygraphy and diagnostical polysomnography, the patients were assigned to groups according to classification criteria.
Results: Findings of the questionnaire survey and tests at the Sleep Diagnostics Centre: preclinical OSAS: 6,017; mild OSAS: 3,609; moderate OSAS: 2,788; severe OSAS: 2,395. Of these persons, 5,286 patients had been treated for hypertension. Using the Pearson chi-square test to identify any connection between hypertension and severe OSAS within the sample, it was possible to conclude that the prevalence of hypertension is not unrelated to the extent of severity of OSAS (df: 3, p: 0.0001, Relative Risk: 1.58). Severe OSAS was diagnosed in 2,395 patients. Of them, 1,441 patients (60.16%) had already received some kind of antihypertensive therapy. In this patient group, 146 persons (7.16%) had cerebrovascular or cardiovascular complications; 693 patients (34.0%) complained of cognitive deficiency.
Conclusion: Based on the prospective study, persons with severe OSAS have a one-and-a-half times greater risk of suffering from hypertension as compared to patients with mild or preclinical OSAS.

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Upper Airway (UA) Mechanical Loads and Neuromuscular Responses Predict Obstructive Sleep Apnea (OSA) Susceptibility

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Introduction: OSA has been associated with alterations in UA mechanical properties and/or disturbances in neuromuscular control. Previous findings indicate that mechanical loads can be quantified with measurements of critical pressure (Pcrit) under conditions of reduced UA neuromuscular activity, and lead to UA obstruction when the passive Pcrit exceeds a threshold of -4cmH2O. In contrast, compensatory neuromuscular responses can mitigate UA obstruction when maximal inspiratory airflow increases by > 200ml/s (ΔVImax). We hypothesized that OSA susceptibility is determined by UA mechanical loads and compensatory neuromuscular responses, and predicted that: (a) the combination of an elevated passive Pcrit (> -4 cmH2O) and diminished ΔVImax (< 200 ml/s) discriminates between subjects with and without OSA, and that (b) decreases in passive Pcrit and/or increases in ΔVImax predict remission of OSA following weight loss.
Methods: During stable NREM sleep, nasal pressure was manipulated to determine the passive Pcrit during brief, stepwise reductions in nasal pressure (PN), and time-dependent compensatory increases in airflow (ΔVImax). These parameters were compared for subjects with (n=29) and without OSA (n=20), as defined by a NREM apnea-hypopnea index of > 10/hr. OSA susceptibility was defined a priori as a passive Pcrit > -4 cmH2O and ΔVImax < 200 ml/s, and OSA resistance was defined by a passive Pcrit below and/or a ΔVImax above these thresholds. Chi-square analysis was utilized to compare frequencies of OSA in susceptible and resistant groups, and a contingency table was used to calculate sensitivity, specificity, and positive and negative predictive values. Changes in passive Pcrit and ΔVImax were also examined for 4 subjects before and after weight loss of 32.5+20.3 kg (BMI decreased by 11.1 + 6.3 kg/m2).
Results: OSA prevalence was significantly increased ($\chi 2$ $p < 0.001$) in susceptible compared to resistant groups (89% vs. 19% prevalence). Contingency analysis revealed that UA characteristics conferred susceptibility with a sensitivity of 86% and specificity of 85%. These characteristics also predicted OSA with a positive predictive value of 89%, and excluded OSA with a negative predictive value of 81%. Only 3 susceptible subjects and 4 non-susceptible subjects were misclassified. Passive Pcrit and ΔVImax responses to weight loss demonstrated decreases in passive Pcrit without any change in ΔVImax (n=2), and concomitant reductions in passive Pcrit and increases in ΔVImax (n=2). OSA remission was associated with reversion from the susceptible to resistant UA 'phenotype' (n=1).
Conclusion: Our findings indicate that discrete separately quantifiable UA characteristics describe: (a) OSA susceptibility based on the degree of elevation in passive Pcrit and the extent to which DVImax is diminished, and confer (b) resistance to OSA when passive Pcrit is reduced and/or DVImax is elevated. These data imply that increased mechanical loads and blunted neural responses are both required for the development of obstructive OSA. Preliminary findings with weight loss further implicate obesity in the pathogenesis of OSA through its effects on UA mechanical loads and compensatory neuromuscular responses.

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Characteristics of Patients with Sleep Disordered Breathing and Diaphragm Paralysis

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Introduction: A recent retrospective analysis of 162 patients diagnosed with uni- or bilateral diaphragm paralysis (DP) revealed that all of 43 patients evaluated with overnight oximetry had abnormal oxygen saturation tracings. This finding suggests a high prevalence of sleep disordered breathing (SDB) in this patient population. Based on animal data and case reports it is common medical practice to evaluate patients with bilateral diaphragmatic dysfunction for nocturnal hypoventilation. Experimental animal data suggest that isolated unilateral DP has no impact on nocturnal breathing and patients with that condition are not generally screened for SDB. We sought to determine clinical risk factors predicting SDB in patients with unilateral DP.
Methods: With IRB approval, we retrospectively reviewed the medical records of 162 consecutive patients diagnosed with DP between January 1994 and December 2000 (123 with unilateral DP, 39 with bilateral DP). Eighteen of these patients underwent polysomnography (PSG). We extracted available clinical, pulmonary function, ambulatory oximetry, and polysomnographic data and compared characteristics of patients undergoing PSG with those not sent for PSG.
Results: Of the 18 patients undergoing PSG, 7 had bilateral and 11 unilateral DP. Indications for PSG included abnormal overnight oximetry (4), clinical suspicion of obstructive sleep apnea (OSA) (9), central sleep apnea(1) or nocturnal hypoventilation (7). Nocturnal hypoventilation was diagnosed in all patients with bilateral and 7 patients with unilateral DP. OSA was found in 7 patients with unilateral and 3 patients with bilateral DP and was the primary diagnosis in 3 patients with unilateral DP. The clinical suspicion of OSA was confirmed in 7 of 9 patients with unilateral DP. In patients with bilateral DP, OSA was suspected in none but diagnosed by PSG in 3 patients. Patients with unilateral DP and nocturnal hypoventilation (Group 1) had significantly higher BMI (37.6 ± 6.6 kg/m2) and PCO2 (41.4 ± 7 mm/Hg) compared with patients with unilateral DP not referred for PSG (Group 2) (30.2± 5.6 kg/m2, p=0.0023 and 50.3 ± 8.3 mm/Hg, p=0.0072 respectively). Functional vital capacity (FVC % predicted) was lower in Group 1 (42.4 ± 12.7) compared to Group 2 (59.9± 12.8, p=0.00265) and there was a trend towards fewer associated comorbidities (significant neurologic, cardiac, pulmonary diseases, OSA and obesity, p= 0.097). Patients with bilateral DP and nocturnal hypoventilation (Group 3) had a lower BMI (28.5±5.4 kg/m2, p= 0.0186) but similar FVC and pCO2 compared with Group 1

(p>0.05). The PSG findings resulted in therapeutic interventions in all 7 patients with bilateral and in 9 of 11 patients with unilateral DP.
Conclusion: PSG has significant therapeutic implications for patients with unilateral DP and clinically suspected SDB or abnormal overnight oximetry. Some patient with bilateral DP had OSA when not clinically anticipated. High BMI, elevated arterial pCO2, decreased FVC and comorbidities are associated with nocturnal hypoventilation in patients with unilateral DP, even when not clinically suspected. We propose that clinicians consider PSG in such patients. The role of PSG in the remaining patients with unilateral DP requires further investigation.

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Results Of Tonsillectomy For Obstructive Sleep Apnea Hypopnea Syndrome In Adults With Tonsillar Hypertrophy

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Introduction: High surgical success rates for adenotonsillectomy in children with sleep-related breathing disorders have been described in various studies. The purpose of the present study were to observe how often a substantial tonsillar hypertrophy is associated with obstructive sleep apnea hypopnea syndrome (OSAHS) in adults and to evaluate the efficiency of bilateral tonsillectomy.
Methods: Data from a retrospective study with 19 adults (sixteen males, three females; average age 32.4 ±8.0 years old ; average body mass index ,27.7 ±5.5 kg/m2) who underwent tonsillectomy as single treatment for sleep-related breathing disorders were evaluated based on the hypertrophy level . The level of tonsillar hypertrophy was rated according to Mackenzie's classification. (Type 2 of Mackenzie's classification is that the tonsil is over posterior pillar and reaching between posterior pillar and midline. Type 3 of it is that both tonsils are very close to midline and likely to contact each other.) Within 2 years , 19 patients with a substantial tonsillar hypertrophy (2 or 3in Mackenzie's classification) underwent tonsillectomy attended polysomunography. Postoperative complications and polysomunographic findings were reviewed. in 3 to 6 months after surgery.
Results: The surgical response rates (defined as decrease in the postoperative AHI ≥ 50%) were totally 63% ,53.3% in 2 and 75 % in 3. No serious complications occured
Conclusion: In the carefully selected patient , a tonsillectomy should be considered an effective and safe surgical option for the treatment of OSAHS.

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C-Reactive Protein (CRP) In Patients With Obstructive Sleep Apnea Syndrome

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Introduction: Obstructive sleep apnea syndrome (OSAS) is associated with cardiovascular morbidity and mortality. Inflammatory processes associated with OSAS may contribute to cardiovascular morbidity in these patients. C-reactive protein (CRP) is an important serum marker of inflammation. We tested the hypothesis that patients with OSAS have increased plasma CRP.
Methods: We studied 53 patients with OSAS (apnea-hypopnea index: AHI > 5) who were free of other diseases We compared CRP levels of OSAS patients with the level of 21 control subjects (AHI <5) who were matched for age and body mass index. The presence and severity of sleep apnea were determined by standard overnight polysomnography.
Results: Plasma CRP levels were significantly higher in patients with OSAS than in controls (2.03+/-0.15 versus 0 mg/dL, p = 0.02). There was a significant positive relationship between CRP and AHI (r =0.25, P =0.03).
Conclusion: OSAS is associated with elevated levels of CRP, as a marker of inflammation and cardiovascular risk.

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Performance Vigilance Task In Patients With Sleep-Disordered Breathing

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Introduction: Altered vigilance performances have been documented in patients with sleep-related breathing disorders (SRBD). Sleep fragmentation, sleepiness, respiratory disturbances and nocturnal hypoxaemia have been suggested as the pathogenesis of these deficits, yet it remains difficult to find a good correlation between performance deficits and the above factors. In the present study we examined which performance measure better characterized SRBD patients and the main factors implicated in these disturbances.
Methods: The study group consisted of 152 patients and 45 controls, all examined with a performance vigilance task and subjective sleepiness assessment every two hours from 9.00 AM to 17.00 PM. Objective daytime sleepiness was assessed in the patient group with the Maintenance Wakefulness Test (MWT). The patients, 53 females and 99 males, aged 52.9 years, with a mean BMI of 31.4 Kg/m2, a mean neck circumference of 41.1 cm, had a mean AHI of 37.7. The controls, 10 women and 35 men, aged 42.8 years, mean BMI 25.2,mean neck circumference 33.1, were free of sleep disorders. The following PVT variables were considered: the mean reaction time (RT) calculated only from correct responses as a measure of speed; the standard deviations of the intra-individual RT (RT variability) used as a measure of performance variability; the number of false responses (RT less than 50 msec), and the number of lapses (RT greater than 1000 msec) as measures of performance accuracy.
Results: Analysis of variance for repeated measures showed no main effect of time-of-day for SSS and VAS and no interaction, controls and patients showing a similar trend. The ANOVA for repeated measures revealed no significant time-of-day effect and no interaction for any PVT measures, RT, RT variability, lapses and false responses showing considerable uniformity in controls and patients. Since no strong time of day variations in sleepiness and PVT measures were present for the control as well as for patient groups, the data of the five sessions were pooled to obtain a mean diurnal value of all sleepiness and PVT measures. Statistical analysis revealed that SRBD patients had worse mean RT scores (p=0.01) when compared to controls, without differences in subjective estimates of sleepiness, i.e., SSS and VAS, and in RT variability. A trend to progressive worsening in RT and RT variability was noted among patients with differences, however, not reaching statistical significance. Overall, control subjects made fewer errors than patients with SRBD, with a significant and strong rise in lapses (p=0.004) in patients with severe OSA. While speed and variability in reaction time were mostly influenced by mean sleep latency at the MWT and subjective sleepiness, sleep fragmentation, nocturnal hypoxaemia and AHI affected mainly PVT accuracy.
Conclusion: Our results suggest that: 1) vigilance impairment, sleep fragmentation and severity of the disease may differentially contribute to the diurnal performance consequences found in SRBD; 2) Since the

PVT worsening is more marked on accuracy that on speed, measurement of lapses and false responses would better characterize the degree of diurnal impairment in these patients.

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Plasma Homocysteine Levels In Obstructive Sleep Apnea Syndrome

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Introduction: Obstructive sleep apnea syndrome (OSAS) is associated with cardiovascular morbidity and mortality. Plasma levels of homocysteine are also associated with cardiovascular morbidity and mortality. We aimed to investigate homocysteine and conventional cardiovascular risk factors in OSAS patients with and without hypertension (HT).
Methods: Levels of homocysteine, cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides were measured in 74 participants after overnight fasting. These included OSAS patients (apnea-hypopnea index: AHI ? 5) with HT (n:15) or without HT (n:38). Control group was employed healthy control subjects without OSAS (AHI < 5) (n:21). The presence and severity of sleep apnea were determined by standard overnight polysomnography. The patients were divided according to their AHI values into mild (AHI: 5-15), moderate (AHI: 16-30) and severe (AHI>30) groups.
Results: After adjustment for age, body mass index, severe group of OSAS patients had significantly higher homocysteine levels than control group. No differences in homocysteine levels were found between OSAS with and without HT groups. No differences in conventional cardiovascular risk factors were found between groups.
Conclusion: Patients with severe OSAS have elevated homocysteine levels. We hypothesize that these results may be explained by endothelial dysfunction combined with excessive free-radical formation in OSAS patients.

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Improvement of Compliance to Continuous Positive Airway Pressure Therapy in Patients with Pressure Intolerance

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Introduction: Continuous positive airway pressure therapy (CPAP) is the treatment of choice for obstructive sleep apnea syndrome (OSAS). Although CPAP is therapeutically effective, the patient compliance is not usually good enough largely because of pressure intolerance. The fact is that the aim of CPAP titration is to determine the pressure which eliminates all obstructive events in all stages of sleep and all positions of the patient. Sometimes this particular level of pressure is found to be intolerant by the patient during the subsequent nights. The purpose of this study was to determine the magnitude of this problem and to decide if it is possible to increase the compliance to CPAP therapy by slight decrease of the treatment pressure.
Methods: A total of 221 consecutive patients diagnosed with moderate to severe OSAS (apnea/hypopnea index [AHI] > 20) served as subjects. There were 205 men, 16 women, mean age 55.3±7.2 years mean AHI = 46.3±12.4. Diagnosis of OSAS was made by all-night full polysomnography (PSG). After diagnostic PSG and CPAP titration all patients continued CPAP therapy at home. If the patient discontinued the treatment during the following two weeks he of she was asked to complete a questionnaire and mark the main reason of discontinuation. In the dropped out patients with main complaint of pressure intolerance the set pressure was decreased by 2 cm and the treatment was initiated once more. The rate of discontinuation was evaluated during the next 2-week period.
Results: 31 out of 221 patients (14.0%) discontinued the treatment because of the main complaint of pressure intolerance. After the decrease of treatment pressure by 2 cm and reinitiating the CPAP therapy 13 of 31 patients (41.9%) successfully completed the next two-week period of treatment.
Conclusion: Effective pressure determined by CPAP titration can be intolerable in some patients during the following course of CPAP treatment. It is possible to improve short-term compliance to CPAP therapy by the slight decrease of the treatment pressure (by 2 cm) in patients with pressure intolerance.

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Flow Volume Loop Features In Obstructive Sleep Apnea

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Introduction: The upper airway dysfunction of obstructive sleep apnea (OSA) has been variably described to have the following two spirometric flow volume loop features-a) a Forced Expiratory Flow {FEF}(50 percent)/Forced Inspiratory Flow {FIF}(50percent) ratio greater than 1 and b) an inspiratory or expiratory flow oscillations i.e.saw-tooth appearance.We studied the flow volume loops of patients diagnosed with OSA.
Methods: Patients with OSA (apnea-hypopnea index >5 diagnosed by overnight polysomnogram) who had spirometry were analyzed retrospectively. FEF50%/FIF50% ratio was computed from the flow volume loops and the loops were visually inspected for inspiratory or expiratory flow oscillations.
Results: OSA was diagnosed in 2090 patients on the basis of overnight polysomnography at the Cleveland Clinic Foundation between 1/2/2001 to 3/1/2003. Out of them, 402 patients had spirometry measurements. FEF50%/FIF50% >1 was seen in 110/402(27%) flow volume loops. Inspiratory or expiratory flow oscillations were seen in 54/402(13%) flow volume loops. Spirometric features of FEF50%/FIF50% >1 or flow oscillations were present in 145/402(36%) whereas both FEF50%/FIF50% >1 and flow oscillations were found in 19/402(4.7%).
Conclusion: Spirometric flow volume loop features of FEF50%/FIF50% >1 and/or inspiratory or expiratory flow oscillations in patients getting pulmonary function tests should elevate the suspicion for underlying OSA and may lower the threshold to order further testing.

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Prospective Study on The Treatment of 328 Consecutive Patients with Obstructive Sleep Apnea Syndrome with A Dental Appliance as A First-line Choice

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Introduction: Dental appliances are alternatives to CPAP treatment and it is possible to use them as a first-line therapy. However, no large-scale investigation in this regard has ever been reported. During the six-year period from 1994 to 1999, we used a dental appliance (DA) as a first-line treatment in all the full PSG-diagnosed OSA patients with an AHI

of more than 10, except those who met the exclusion criteria.
Methods: During the six-year period, overnight PSG was performed on 737 new patients, 488 of whom were found to have an AHI of more than 10. Among them, 67 were excluded according to the exclusion criteria . Four hundred and twenty one patients were invited to the study. Among them, 93 patients refused DA treatment and were put on CPAP or upper airway surgery. Altogether 328 patients were entered to the study, regardless of their disease severity and degree of obesity. The criteria for a good responder is that AHI should be decrease by more than 50% and should be below 20 with the DA in place. After three months use of the DA, a follow-up full PSG was done in all the patients. Good responders continued with the use of DA. Follow-up PSG was performed one or several years later whenever possible.
Results: The evaluation of the treatment response was made on 320 cases, among which 54% were good responders. The response rate remained over 60% in patients with an AHI of as high as 50. In patients with an AHI of over 50, the response rate decreased to 35.9%. We found that although the response rate decreased as BMI went up, even in patients with a BMI of more than 30, the response rate was as high as 43.9%. In good responders, treatment with the DA resulted in a significant decrease in stages one and two sleep and a significant increase in delta and REM sleep. After the treatment with the DA, significant improvement in Epworth sleepiness scale scores was found not only in good responders, but in poor responders as well. This is also the case with snoring score. No severe complications were observed. The compliance to treatment in good responders was 90% after one years treatment and remained to be 70% after 5 years.
Conclusion: DA should have the role as the first-line choice in the treatment of OSA.

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Reciprocal Interactions Between Spontaneous And Respiratory Arousals In Adults With Suspected Sleep-Disordered Breathing

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Introduction: Excessive daytime sleepiness (EDS) is a major consequence of sleep disordered breathing (SDB) in adults, leading to a significant deterioration in mood and neurocognitive function. In a large cohort of snoring children, spontaneous and respiratory arousals display reciprocal interactions, and led to development of a new quantitative measure, the Sleep-Pressure Score (SPS), which may provide a useful intrapolysomnographic estimate of sleep pressure in snoring children. We therefore aimed to investigate interactions between respiratory and spontaneous arousals in adults with suspected SDB, and to examine potential correlations between SPS and the Epworth Sleepiness Score (ESS).
Methods: Chart review on 145 consecutive patients evaluated for SDB at 2 sleep centers.
Results: 145 patients (57% male) with mean age of 43.7+/-12.0 years and mean BMI of 37.8+/-9.8 kg/m2. A significant correlation was found between respiratory arousal index (RAI) and AHI (r= +0.98, p<0.0001), whereas an inverse correlation between the spontaneous arousal index (SAI) and AHI (r= -0.44, p<0.0001) emerged. Based on such findings, the SPS was calculated for each patient [SPS=(RAI/total arousal index) * (1-SAI/total arousal index)]. SPS values exhibited an AHI-dependent exponential behavior with saturation at AHI values ?55/hrTST. As in previous studies, no correlation was found between the ESS and AHI. Similarly, ESS and SPS were unrelated.
Conclusion: Adults with SDB exhibit reciprocal interactions between respiratory and spontaneous arousals, that can be expressed by a numerical factor, SPS, that is closely linked to the severity of SDB when expressed as AHI. These interactions may reflect homeostatic mechanisms for preserving sleep structure in patients with SDB. We propose that SPS may provide a useful approach to assess sleepiness and its morbidity correlates in SDB.

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Elevated Cytotoxicity and Cytokine Imbalance as Markers of Lymphocyte Activation in Sleep Apnea Patients. Effects of nCPAP Treatment

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Introduction: Obstructive sleep apnea (OSA) constitutes an independent risk factor for cardiovascular morbidity and mortality. T cells play a significant role in atherogenesis partly due to the secretion of pro-atherogenic cytokines and by participation in endothelial cell injury and plaque development. We hypothesized that intermittent hypoxia and sleep fragmentation could induce lymphocyte activation, which may be implicated in the pathogenesis of atherosclerosis in OSA patients. To support our hypothesis we evaluated the cytotoxic potential and phenotype of three T cell subsets, studied their TNF-α/IL-10 ratio, and determined the effects of nasal continuous positive air pressure (nCPAP).
Methods: CD4, CD8 and γδ T cells were isolated by magnet separation from peripheral blood of 37 OSA patients (age 52.1±11.5, BMI 29.1±5.3, RDI 28.8±13.7) and 18 controls (age 46.4±10.5, BMI 25.7±6.9, RDI 10.5±4.0).The phenotype and cytokine profile were analyzed by flow cytometry. Cytotoxicity against Human Umbilical Vein Endothelial cells (HUVECs) was assessed by 51Cr release assay.
Results: The cytotoxicity of CD8+, CD4+ and γδ T cells from OSA patients against HUVECs was about 2-fold higher compared to controls. Cytotoxicity of CD8+ T cells was directly dependent on the presence of CD56/CD16 natural killer receptors and cytoplasmatic perforin, and could be abolished by removal of CD56+/CD16+/Perforin+ T cell subset (45.3±16.7% vs. 4.6±2.3%, p=0.0001). This cytotoxicity was also positively correlated with RDI and with increased expression of CD40L. By contrast, perforin-containing granules were infrequently detected in OSA CD4+ T cells, but the size of CD4+/CD28null population, a plaque-infiltrating highly cytotoxic subset, was increased in the patient group (19.1±5.1% compared to 7.1±1.5% in controls, p=0.004). Also, the increased cytotoxicity of OSA γδ T cells did not depend on the expression of CD56/CD16 but could be abolished by addition of anti-TNF-α antibodies. Moreover, in all patients studied γδ T lymphocytes expressed altered pro-inflammatory/anti-inflammatory cytokine balance i.e. TNF-α expression was increased by 3.8-fold, whereas IL-10 expression was decreased. Such cytokine imbalance was observed in CD8+ and CD4+ T cells only in 30% of OSA patients. In all lymphocyte subsets however IL-10 expression was inversely correlated with RDI. nCPAP treatment significantly lowered the cytotoxicity (p=0.01), the expression of CD56 (from 48.6±14% to 36.9±17%, p=0.03), CD40L (from 16.2±10% to 4.0±2.9%, p=0.01) and TNF-α (from 8.1±6.0% to 2.8±2.2%, p=0.009) in CD8+ T cells, but had no effect on CD4+ T cell phenotype and functions.
Conclusion: Despite the differences in mechanisms of cytotoxicity observed in the various T cell subpopulations, each of the T cell subgroup studied could contribute to endothelial cell damage through enhanced cytotoxicity. The differences observed in cytokine production between CD4, CD8 and γδ T cells of OSA patients may indicate that var-

ious T cell subsets respond differentially to a given stimulus of intermitted hypoxia and/or sleep fragmentation, and γδ T cells were the most sensitive responders. Hence, pro-atherogenic lymphocyte activation constitutes a risk factor for atherosclerosis in OSA. nCPAP treatment can ameliorate some lymphocyte dysfunctions and thus block some of the pathways that promote atherosclerosis in OSA patients.

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Neuropsychological Assessment of Patients Treated For Obstructive Sleep Apnea Syndrome

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Introduction: It is an established clinical finding that patients suffering from obstructive sleep apnea syndrome (OSAS) have impaired mental functions and chronic vascular disease entities. This study had the objective to identify cognitive functions of patients with OSAS following diagnosis of the condition, and subsequently, to see if measurable change in cognitive function occurs before and after (12-18 months) nasal CPAP therapy.
Methods: In the first stage, the battery of tests was made up, in keeping with international professional literature, of 25 tests that were primarily sensitive to frontal and parietal function. Based on initial experiences, the following tests were retained: personality profile (MMPI test); mood (Beck Depression Scale); intellectual level (Benton Visual Retention Test); handwriting fluency (writing upon dictation); calculation fluency (basic arithmetic operations mentally and in writing); visual memory (Benton Visual Retention Test); incidental visual memory (Rey Complex Figure Test and Recognition Trial); verbal memory (Ranschburg-Ziehen word-pairs, learning of 8-item word lists, digit span test, sentence writing on dictation, attention/psychomotor tempo, accuracy, choice reaction time, fatigability (Pieron Test), concrete spatial orientation-task organization (Floor plan viewed from above), constructive practice (Drawing test), dynamic practice (performance of series of movements with 2x3 elements, change with right and left hand), the synchronous-opposite innervation of the two hemispheres (test requiring reciprocal coordination of both hands), executive function-visuospatial construction (Rey Complex Figure). Patients: number of patients studies: 14; sex: male; mean age:55.4 years, SD:5.7 years, age range: 48-70 years.
Results: Follow-up tests carried out 1 year after CPAP treatment showed significant improvement in the following areas: 8-element word list-immediate recall (Wilcoxon test, p:0.029). Beck Depression Scale total score (Wilcoxon test p=0.016), Dynamic practice-left hand (sign test p=0.063), Dynamic practice-right hand (sign test p=0.008), writing test (sign test=0.063), Pieron test-choice reaction time (Wilcoxon test, p:0.075), Rey Complex Figure-reproduction (Wilcoxon test, p:0.042).
Conclusion: Our results show that if patients performance is studied prior to CPAP therapy, disturbances could be seen primarily in frontal-premotor functions with parietal functions being unaffected in the tests administered. In the course of correct CPAP treatment significant improvements could be found in several functions of the patients mental achievement: dynamic practice, verbal learning, incidental visual memory-task organisation, psychomotor tempo, auditory vigilance-sound analysis as well as in the field of subjective symptoms. It seems fair to conclude for the analysis of data that functional disturbances present in the frontal-attention-concentration-memory processes of patients suffering from obstructive sleep apnea, with their mood, general feeling, daily activity and efficiency deteriorating. These problems tend to improve, or even eliminate, once correct CPAP treatment is administered.

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Comparison of Daytime Sleepiness and Function Pre- and Post-CPAP Treatment Among Levels of Sleep Apnea Disease Severity and Normal Controls

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Introduction: Clinical trials have demonstrated that CPAP is efficacious in improving daytime sleepiness and functional status in OSA. However, there is little evidence of the degree of impairment compared to normal functioning and the magnitude of post-treatment improvement relative to disease severity. Thus, the aims of this multicenter study were to 1) describe OSA pre-treatment deficits in sleepiness and functional status compared to normal controls and 2) compare the magnitude of post-treatment improvement relative to 3 levels of disease severity and normal controls.
Methods: 159 OSA patients (mean age 46.53; 83% male) at 7 sites in US and Canada were recruited from clinical practice. Inclusion criteria were age 21 to 60 years, an AHI > 20 per hour, clinical judgment of excessive daytime sleepiness, and candidate for CPAP treatment. Anyone with another co-existing sleep disorder, history of sedative-hypnotic use, cerebrovascular accident, COPD or other pulmonary disease, or CHF was excluded from the study. OSA patients were grouped by disease severity (AHI 20 to <40, n=42; AHI 40 to <60, n=29; and AHI >60, n=95). Thirty-four interview and PSG-screened (AHI < 5) normal controls (mean AHI .55; mean age 41.7 years; 65% male) were recruited from the community. During one day of testing in the laboratory, patients (pre-treatment) and the normal controls completed the Epworth Sleepiness Scale (ESS), Multiple Sleep Latency Test (MSLT), Functional Outcomes of Sleep Questionnaire (FOSQ) (to measure disease-specific functional status), and Sickness Impact Profile (SIP) (to measure generic functional status). After 3 mo of monitored CPAP treatment, patients again completed the same measures.
Results: At baseline, all three patient groups were significantly more impaired on the MSLT, ESS, and FOSQ than the normal group ($p < .05$ on all measures). There were no differences between the normal controls and the three groups on the SIP. Mean CPAP mask-on use for the pooled patient sample was 4.93 + 2.05 hours, and for the three groups was 4.92, 4.32, and 5.15 hours, respectively ($p = .21$). Patients improved on all measures (except the MSLT) following treatment, with robust effect sizes (ESS effect size .72-1.43, FOSQ effect sizes .64-1.13, SIP effect sizes .74-.95). Only the most severely affected had a significant change post treatment on the MSLT (normals: 12.04 min; mild: baseline 8.11 min, posttreatment 8.65 min; moderate: baseline 7.14 min, posttreatment 8.42 min; most severe: baseline 6.03 min, posttreatment 9.37 min, mean change 3.34 min, effect size .73) For all outcomes, the most severe patient group experienced the greatest change. Following treatment, the three patient groups no longer significantly differed from each other or from the normal controls on the ESS and MSLT, but the FOSQ total scores for the least severe group (mean 16.62) significantly differed from those of the normal controls (mean 18.33) and from the two higher AHI patient groups (means 17.87 and 18.13, respectively). On the SIP, all three patient groups had better scores following treatment than the normal controls, but this difference was not significant.
Conclusion: OSA substantially affects patients daytime daily functioning. CPAP treatment mitigates this impairment, alleviating sleepiness and restoring daily functioning to levels similar to normal individuals, with greater effects in the more severely affected. OSA substantially affects patients daytime daily functioning. CPAP treatment mitigates this

impairment, alleviating sleepiness and restoring daily functioning to levels similar to normal individuals, with greater effects in the more severely affected.

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Cheyene Stokes Respiration and Congestive Heart Failure. Is it Underdiagnosed?

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Introduction: Cheyne-Stokes respiration with central sleep apnea (CSR) is a form of periodic breathing in which periods of apneas and hypopneas alternate with periods of crescendo-decrecendo tidal volume. Patients with CHF may be predisposed to periodic breathing because of increased chemosensitivity, hyperventilation, and prolonged circulation time. In fact CSR has been reported to be present in 30-40% of patients with CHF and a left ventricular ejection fraction of <45%. In addition CSR has been reported to be an independent risk factor for increased overall mortality in patients with CHF. Treatments have included nocturnal oxygen, various forms of positive airway pressure as well as pharmaceutical treatments. We reviewed Polysomnograms (PSGs) and Echocardiograms (Echo) to determine prevalence and characteristics of patients with CSR in the setting of an integrated tertiary care center. In addition, we report here our success to therapy attempts initiated at the time of recording.
Methods: The PSGs recorded consecutively from 2002-2003 (n=3779) were screened for the presence of CSR. Polysomnography included transcoronal EEG, low light video, oral and nasal airflow with thermocouple, electrooculogram, chin electromyogram, chest and abdominal movement, oximetry, two lead electrocardiogram, and body position. Sleep staging was performed according to the R & K scoring manual. CSR was identified when the central events were preceded and terminated with a crescendo-decresendo pattern of tidal volume. The results of baseline polysomnography and subsequent therapeutic studies in addition to demographic data, medical history including the presence of cardiovascular disease, and Echo data (when available) were reviewed.
Results: The findings of 3779 PSGs were screened. CSR was identified in 30 patients (0.8%) The median age was 63 years (range, 33-83). Twenty-two patients were male (73%) with a median BMI of 31.9 kg/m2 (range, 20-89). Referrals were from primary care (33%), cardiology (30%), pulmonary (13%) and sleep medicine (10%). A history of cardiovascular disease was present in 93% of patients while 14 patients (50%) carried a clinical diagnosis of CHF. The median AHI was 51.5 events/hr (range, 12-145). Most patients (25) had some therapeutic intervention including supplemental oxygen therapy, CPAP or BIPAP. Improvement was noted in 15 patients (CPAP success in 9, BIPAP in 3 and O2 in 3). Multiple studies were required in 8 patients to determine optimal treatment combinations. Echo data was available in 20 patients. Upon review two groups of patients with CSR were identified. One group of 8 patients (40%) had evidence of left ventricular systolic dysfunction (EF<40%). In the second group (12 patients) mild-moderate left ventricular hypertrophy was present without evidence of left ventricular systolic dysfunction.
Conclusion: In this study we identified 30 patients with CSR (<1% of all PSGs). Successful therapy was possible at the time of recording in over 50%. Given the evidence of decreased mortality and improved quality of life in treated CSR identification of those at risk is important. Patients with CSR had evidence of either systolic dysfunction or mild-moderate left ventricular hypertrophy. In the two largest studies to date only patients with systolic dysfunction were evaluated for the presence of CSR. This study suggests the need for PSG evaluation for the presence of CSR in all patients with CHF and not only in those with left ventricular systolic dysfunction.

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The Relationship Between Cigarette Smoking And Obstructive Sleep Apnea In Brooklyn Population

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Introduction: The role of Cigarette smoking in obstructive sleep apnea remains unsettled. Some investigators reported that smoking is an independent risk factor for OSA while others reported that it is not. To our knowledge, no studies addressed any race-dependent effects of smoking on OSA. In this study we examined the effect of smoking on OSA in a population that mainly consists of African Americans(AA) and Hispanics(H) with some Caucasians(C) included.
Methods: This is a randomized retrospective case-control study in which all the patients referred to the Sleep Laboratory in Kings County Hospital at Brooklyn, NY from January 2002 to October 2003 were included. The total number of the patients was 307(154 M, 153 F; mean age 47.47 years, SE = 0.72 ; mean BMI 41.72 Kg/m(2), SE = 0.71; race 73.9% AA, 18.6% H, 7.5% C; 70.7% with AHI of 15 or more, 29.3% with AHI less than 15). We categorized the total population as well as each race separately into smokers and non-smokers to examine if there is any significant difference in the prevalence of OSA among any of the groups. An AHI of 15 or more was chosen as the cutoff value to consider the patient as having OSA. Using multivariate model we adjusted for Age, Sex, Race and BMI to examine the effect of smoking on OSA, then for Age , Sex and BMI to examine any race-dependent effect of smoking on OSA.
Results: Using univariate statistics(Chi-Square), OSA with an AHI of 15 or more was more prevalent in smokers than in non-smokers(P=0.040).AA who smoke had higher prevalence(P=0.021) of OSA than Hispanics or Caucasians who smoke(P=0.788 and P=0.680 respectively).However, using multivariate model while adjusting for Age, Sex, Race and BMI, the effect of smoking on OSA was not statistically significant in the total population(P=0.779) . There was no statistically significant race-dependent effect of smoking on OSA when comparing AA and Caucasians(P=0.989) or Hispanics and Caucasians(P=0.536).The inability to find significant effects for the interaction of smoking and race might have been due to the lack of power produced by the small number of Caucasian population. Therefore, we assessed smoking as a risk factor for OSA after adjusting for other risk factors (Age, Sex and BMI) in AA subjects only. We found that smoking was not a significant predictor for OSA in this AA population(P=0.377).
Conclusion: Cigarette Smoking is not an independent risk factor for obstructive sleep apnea in a population that consists mainly of African Americans and Hispanics.

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Nightly Variability of Sleep-Disordered Breathing Measured Over Three Nights

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Introduction: The amount of nightly variability that occurs in sleep-disordered breathing (SDB) is a topic of considerable controversy in the field of sleep medicine. Studies have primarily focused on the variability of SDB across two nights, which has provided conflicting results with misclassifications occurring in 6% to 54.5% of patients when using an AHI cut-off of 5. The majority of these studies were based on small sample sizes. Of the studies with more than 90 subjects, 1) LeBon et al (2000) tested SDB on sequential nights in the sleep laboratory, finding a first night effect with the AHI being lower on night 1 vs. night 2; and 2) Quan et al (2002) tested SDB over a mean time interval of 2.5 months in the home, finding 20% misclassification over that time interval. The present study examined the nightly variability of SDB across three nights in the home on a sample of over 1000 participants.
Methods: Participants referred for diagnostic testing of SDB from within the continental United States were included in this retrospective comparison of three nights of recordings performed in the home using the NovaSom QSG (Sleep Solutions, Inc., Palo Alto, CA). The NovaSom QSG software analysis algorithm defines apnea as cessation of airflow for > 10 seconds and hypopnea as a >50% reduction in airflow for >10 seconds that is linked to >4% oxygen desaturation. The apnea-hypopnea index (AHI) is defined as the total number of apneas and hypopneas divided by total hours of recording time. This device has been shown to reliably measure the AHI (Claman et al, 2001 ; Reichert et al, 2003).
Results: 1093 studies were available for analysis with 87% being male. The average recording duration per night was 6.4 +/- 1.2 (range 3.0 - 7.8). The mean AHI on night 1 was 17.9 +/- 20.6 (range 0 - 113.6), on night 2 was 18.2 +/- 20.5 (range 0 - 126.9), and on night 3 was 18.2 +/- 20.9 (range 0 - 108.3). The intraclass correlation coefficient for AHI across the three nights was .90, with the 95% CI ranging from .89 to .91 indicating very high consistency across the three nights of measurement. AHI was not significantly affected by recording duration (F=.817, p=.601). Using the AHI from the first diagnostic testing night, 89.4%, 90.1% and 89.4% of patients were classified consistently with the highest AHI measured across the three nights when using an AHI cut-offs of 5, 10, and 15, respectively. This means that approximately 10% of cases were misclassified based on the first diagnostic testing night relative to the highest AHI across the three nights.
Conclusion: Despite there being a relatively high level of agreement between AHI measured over three nights in the home, these findings suggest that one negative night is not sufficient to rule out a diagnosis of SDB in approximately 1 out of every 10 cases. This study suggests that reliable and reproducible data can be obtained in a home recording setting provided that at least 15-20hrs of recording time is obtained.

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Regulation Of Sleep-Wake States In Response To Intermittent Hypercapnic Stimuli To Mouse Applied Only In Sleep

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Introduction: Hypoxia and hypercapnia may cause arousal and sleep fragmentation in human obstructive sleep apnea syndrome. Recently, several reports presented chronic repetitive ambient hypoxia as a rodent model of sleep-related breathing diseases (SRBD). However, with this model, it is not possible to elucidate the relative roles of hypercapnia as well as hypoxia on sleep and vigilance. Here, we present a mouse model of sleep-induced hypercapnia/hypoxia to assess this question.
Methods: Adult male C57BL/6J mice were surgically implanted with EEG and EMG electrodes for chronic recording of sleep-wake states. After recovery period (> 7 days), 24 hours of base line sleep-wake states were monitored. Then, a computer algorithm detected sleep-wake states by 5 seconds bins and triggered hypercapnia, hypoxia or room air stimuli for 24 hours. Finally, animals were monitored for 24 hours after the stimuli. Hypercapnia was applied by adding CO2 gas and hypoxia by adding nitrogen gas to the room air. Flows of the room air, CO2 and N2 were monitored and controlled by PC (0 to 5 L/min each). As a first step, we applied hypercapnia only during sleep period to three adult mice to detect its effects on sleep.
Results: Sleep-wake states before application of hypercapnia were non-REM: 34.4 ± 3.48%, REM: 5.68 ± 3.12% and wake: 59.9 ± 4.3%. While applying 15% CO2 only during sleep, animals spent significantly more time in awake and less time in non-REM sleep than before ($p < 0.01$ and $p < 0.05$, respectively; non-REM: 19.0 ± 6.3%, REM: 2.14 ± 0.81% and wake: 78.8 ± 5%). After returned to the room air, they spent significantly more time in non-REM sleep and less time in wake comparing to while applying hypercapnia ($p < 0.01$ and $p < 0.01$, respectively; non-REM: 37.7 ± 4.81%, REM: 8.54 ± 5% and wake: 53.8 ± 2.22%).
Conclusion: With hypercapnic stimuli, wakefulness episodes were longer and more frequent. After the stimuli, there was a rebound increase in REM and non-REM sleep and decrease in wakefulness. The results show that sleep-specific hypercapnia leads to significant modulation of sleep-wake regulation both during and after application of the intermittent hypercapnic stimuli during sleep. Further use of this system to hypoxia and/or hypercapnia and the availability of mouse models of SRBD will enhance our understanding of the neurobiological mechanisms underlying the symptoms as well as of the arousal controlling systems.

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Opioid Induced Sleep Breathing Abnormalities. Diagnostic and Therapeutic Features. Dose Dependant Phenomenon ?

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Introduction: Opioid analgesic therapy is increasingly being used to treat chronic pain of "non-neoplastic" etiology. A robust literature has been published about the diurnal respiratory depressant effect of opioids, however, there is a significant lack of information about the ability of opioids to cause special types of sleep breathing disorders (SBD). We describe in this report a set of patients who have distinctive patterns of SBD likely due to opioid use.
Methods: This is a retrospective review of patients who were referred to our sleep laboratory for the work up of sleep apnea and who were actively using opiates at the time of the polysomnography (PSG). Patient charts were reviewed to obtain demographic data, pertinent clinical information and PSG variables to establish the degree of SBD and response to positive pressure therapy. A detailed history about the nar-

cotic use and other neurotropic medications was obtained. Patients were using different opioids i.e. methadone, morphine and oxycodone. All the narcotic doses were converted to "morphine dose equivalent" using published nomograms to establish a relation between opioid dose and severity of SBD. Correlation was established between the Morphine dose equivalent (MDE) per day and the sum of abnormalities noted in each patient. Results are presented as mean ± standard deviation.
Results: Eight patients were identified of which 2 were females. Patient characteristics include: age 51 ± 8.1 years, BMI 33 ± 4.4 kg/m2, Collar size 17.1 ± 1.5 inches, Epworth Sleepiness Score 11.9 ± 6.3 and narcotic use of 69.5 ± 40.8 mg/day of MDE orally (range 15 mg to 120 mg/day). The study population had a Total Sleep Time (TST) (336 ± 59.7 min), Sleep Efficiency (80.8 ± 11.1 %), Sleep Latency (21.3 ± 15.8 minutes), Rapid Eye Movement (REM) Latency (192.9 ± 86 minutes), Non-REM Sleep (88.3 ± 7.2 % of TST) and REM Sleep (11.6 ± 7.2 % of TST). 6/8 patients underwent positive pressure titration studies. Four did not volunteer their narcotic use on the initial sleep history questionnaire. Five patterns of abnormal sleep breathing disorders were identified on the PSG. Central apneas were observed in 4/8 patients, obstructive hypoventilation in 2/8 patients, Bradypnea with Biot breathing in 4/8 patients, improvement of hypoxemia by REM sleep in 1/8 patients and difficulty in controlling respiratory events by positive pressure treatment in 4/6. A high degree of correlation between MDE and the sum of sleep breathing abnormalities per patient was observed ($r= 0.92$, $p<0.01$). No abnormalities were observed in patients taking MDE less than 60 mg/day. One patient on a morphine pump had a repeat study 3 years later, on a reduced dose but the sleep abnormalities were still present.
Conclusion: Opioid therapy can be associated with significant SBD. Response to typical sleep lab therapy may not occur. Any sleep questionnaire should have a specific inquiry regarding narcotic use since patients may not volunteer their narcotic use. Further research needs to be done to characterize the pattern and dose relationships of SBD and opiates.

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Obstructive Sleep Apnea Syndrome Treatment with Intra Oral Mandibular Repositioner Appliances

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Introduction: The use of intra-oral appliances for the treatment of the obstructive sleep apnea syndrome (OSAS) became an important therapy to prevent the collapse of the base of the tongue against the lateral and posterior walls of the pharynx during sleep. The mandible position makes an important influence in the tongue muscle activity, an advanced position for the mandible during sleep, increases the genioglossus muscle activity. The intra-oral appliances for the treatment of OSAS are simple, non invasive, easy to use and of low cost, and they have profit a considerable space in the scientific literature in the present time, being necessary more studies to define the target population potentially more inclined to answer to this treatment.
Methods: 188 previously treated patients with IOMRA had been contacted by telephone and were inquired on their improvement, Fifteen patients had not presented improvement of their main complaint (approximately 8% of those who had been treated) forming our Study Group (SG). Fourteen patients of the remaining 173 had got improvement, and were paired according to gender, age, apnea and hypopnea index as Control Group (CG). The two groups had answered a sleep questionnaire for diagnosis of sleep disorders, Beck for depression, IDATE for anxiety and Epworth Scale for daytime excessive sleepiness. The results had been analyzed with Qui-Square and binary regression analysis to determine if the factors associated to treatment failure differ between SG and CG. We considered significant $p<0.05$.
Results: We have not observed significant differences between SG and CG when we compared just one variable between the two groups, therefore when we analyzed the interaction of 2 variables we could observe comorbities ($p<0.05$) : a) BMI >25kg/m2 and history of surgery were presented in 69% of SG and 50% of CG; b) BMI >25kg/m2 and coffee drinking about 0.5 to 4 cups a day were presented in 67% of SG and 25% of CG; and c) Psychiatric disorders and coffee drinking about 0.5 to 4 cups a day were presented in 80% of SG and 0% CG.
Conclusion: The interaction of BMI, history of surgery, psychiatric disorders and coffee drinking were features associated to patients that presented less improvement with IOMRAs. We believe that before to suggest IOMRA treatment the dentists should be aware of the comorbidities above, what can prevent some futures troubles and unsatisfaction.

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Diagnostic Utility Of Nasal Cytology In Obstructive Sleep Apnea

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Introduction: Nasal inflammation has been associated with sleep-disordered breathing. Inflammatory changes in the nasal mucosa have been implicated as potential impediments to patients responding to treatment with nasal continuous positive airway pressure (nCPAP) therapy and possibly with respect to patient compliance. Cytological changes in the nasal epithelium form the physiological basis of nasal inflammation. We tested the hypothesis that differences in nasal cytology as defined by detection of inflammatory cells (e.g., eosinophils, basophils or neutrophils) can be used to characterize newly diagnosed patients with obstructive sleep apnea (OSA) prior to initiation of nCPAP therapy.
Methods: As part of a larger study that had enrolled 111 OSA patients, 38 newly diagnosed patients were referred from the Scripps Clinic Sleep Center for participation in this protocol. History, physical examination, and allergy skin testing were used to subdivide the participants into 3 categories of no rhinitis (NR), non-allergic rhinitis (NAR), and allergic rhinitis (AR). The participants then underwent nasal scrapes for cytology prior to initiation of nCPAP therapy. Patients were followed by monthly return visits to the General Clinical Research Center as part of the larger study and as a means to assess compliance with nCPAP therapy.
Results: 38 newly diagnosed OSA patients were stratified into NR (n=18), AR (n=14), and NAR (n=6) groups based on history, physical examination, and allergic skin testing. Based on nasal cytology 17 of 18 NR, and 5 out of 6 NAR patients were without eosinophilia or basophila. 10 out of 14 AR patients were symptomatic, and 4 of these had nasal smears that were positive for eosinophils or basophils. The specificity for detecting eosinophils or basophils in the nasal smears of OSA patients with symptomatic AR or NAR was therefore estimated at 94.4%. Out of 15 patients who did not comply with return visits 7 had AR (3 of 7 were neutrophil positive, $P<0.05$), 2 had NAR (2 of 2 were neutrophil positive, $P<0.5$), and 6 had NR (3 of 6 were neutrophil positive). Out of 23 patients that completed the return visits, 12 had NR (7 of 12 were neutrophil positive), 4 had NAR (1 of 4 was neutrophil positive), and 7 had AR (0 of 7 was neutrophil positive, $P<0.05$).
Conclusion: Nasal cytology can be very useful in the diagnosis of nasal inflammation in the patients with OSA. To determine if nasal cytology can be predictive of compliance with nCPAP therapy requires further investigation.

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Sleep Architecture And Periodic Breathing During A Trek From 1400-5000 Metres In The Nepal Himalaya

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Introduction: Sleep at high altitudes has been recorded as being characterised by poor subjective sleep quality, frequent arousal and periodic breathing. Stage 1 nonREM sleep increases, slow wave sleep decreases while REM sleep and total sleep time remain unchanged. It has been suggested that these changes to sleep architecture and subjective sleep quality are due to the development of periodic breathing during sleep at high altitude.
Methods: We performed overnight polysomnography (EEG, EOG, EMG submental, chest and abdominal effort, ECG, anterior tibialis, nasal flow and oximetry) on twenty normal, healthy volunteers (10 male, 10 female), aged from 20-52 years (mean age 34 ± 9 years) at five ascending altitudes during a trek from 1400 metres to 5000 metres in the Nepal Himalaya. Baseline sleep studies were performed at sea level in Sydney prior to the trek.
Results: Sleep architecture changed during ascent with an increase in Stage 1 NREM sleep from a mean of 3.3% at sea level, 4.7% at 1400m, 9.4% at 3500m, 8.8% at 3900m, 8.6% at 4200m and 12.9% at 5000m. There were no significant changes to the percentages of any other sleep stage. Periodic breathing (PB) occurred in sixteen of the twenty subjects but only six subjects had PB at every altitude from 3500-5000m; a further ten had PB at one to three altitudes. Four subjects had no PB at any altitude and one subject developed PB at 1400 metres. The central AHIs varied from 20 to 149/hour. When comparing the sleep architecture of subjects with PB to those without PB there were significant differences in Stage 1 NREM percentage at two altitudes (3900 m p=0.01 and 4200 m p=0.0001). There were no significant differences between periodic breathers and non periodic breathers in any other parameter measured i.e. sleep efficiency, sleep latency or REM latency. Subjective sleep quality varied widely but was related to PB in only one subject at every altitude and in two subjects at 5000m i.e. poor sleep reported as being due to difficulty initiating or maintaining sleep due to repetitively waking gasping.
Conclusion: Sleep architecture remains largely unaltered during ascent from 1400m to 5000m with the exception of the percentage of Stage 1 NREM sleep, which increases with each ascent to higher altitude. Periodic breathing developed in sixteen of the twenty subjects. The development of PB does not significantly alter the sleep architecture nor subjective sleep quality.

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Mortality of Veterans with Sleep Apnea: Untreated versus Treated

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Introduction: Untreated obstructive sleep apnea (OSA) appears to increase mortality. The effect of treatment on mortality rate is unclear because most previous reports analyzed small samples and did not adequately control for comorbidity. We sought to determine whether providing a continuous positive airway pressure (CPAP) device or performing uvulopalatopharyngoplasty (UPPP) is associated with a decreased mortality rate relative to providing no treatment for OSA, in a large cohort with control for comorbidity.
Methods: This retrospective inception cohort study included all patients diagnosed with OSA in any Veteran Affairs (VA) inpatient facility 1991 - 2001 or outpatient facility 1997 - 2001. Subjects were identified by ICD9 diagnostic codes in the VA inpatient and outpatient treatment files. Treatment status (None, CPAP, UPPP, or tracheotomy) was determined by ICD9 or CPT procedure codes in these databases. Patients without a code for CPAP, UPPP, or tracheotomy were considered untreated. Patients undergoing tracheotomy were not included in this analysis, because indications for tracheotomy could not be determined. CPAP patients were provided a CPAP device, but usage data were not available. Sleep apnea severity data were not available. The Charlson Comorbidity Index was calculated from ICD-9 diagnostic codes from the year prior to inception into the cohort. Mortality data were extracted from VA Death Files. Survival time was calculated from the date of first diagnosis of OSA to date of death or 9/30/2002. Treatment groups were compared on mortality hazard with Cox regression, adjusting for age, sex, race, comorbidity, and inception year.
Results: The cohort consisted of 149,267 veterans, age 57+/-12 (mean+/-SD) years, 97% male. By September 2002, 16,967 of 116,678 untreated patients (14.5%), 3256 of 28,612 CPAP patients (11.4%), and 394 of 3977 UPPP patients (9.9%) were dead (untreated v treated, p<0.001). From the date of OSA diagnosis, untreated patients survived 3.6+/-2.3 years, CPAP patients survived 4.6+/-2.5 years, and UPPP patients survived 5.3+/-2.5 years (untreated v treated, p<0.001). After adjusting for the variables listed, untreated patients had 1.9 (95%CI 1.8-2.0, p<0.001) times greater hazard of dying at any time relative to treated patients. UPPP patients had a lesser mortality rate (p=0.006), longer survival (p<0.001), and lesser hazard of death (adjusted hazard ratio 0.57, 95%CI 0.39-0.81, p=0.002) relative to CPAP patients.
Conclusion: Treatment with CPAP or UPPP confers a survival advantage over no treatment, after adjustment for age, sex, race, comorbidity, and year of OSA diagnosis. One cannot draw conclusions about the relative efficacy of CPAP and UPPP because CPAP usage data were not available.

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Determinants Of CPAP Acceptance In OSA Patients

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Introduction: It has been reported that obstructive sleep apnea (OSA) may affect various aspects of quality of life as well as neurocognitive functioning. Although the treatment with continuous positive airway pressure (CPAP) has been shown to improve both the symptoms of apnea and daily function, the acceptance rate of CPAP is relatively low. Subjective sleepiness hs been reported to be a predictor of CPAP acceptance. The present study aims to further explore the factors that may influence the acceptance of CPAP treatment, by measuring the neurocognitive performance, subjective rating of cognitive impairment, sleep parameters, as well as other psychosocial measures in patients with OSA.
Methods: 19 male and 1 female OSA patients, averaged 41.5 (SD=7.11) years old, participated in the study. They were diagnosed with moderate to severe OSA (RDI Mean=59.57, SD=23.69) and hve completed CPAP titration. A package of subjective rating scales was administered, including Epworth Sleepiness Scale (ESS), Medical Outcome Study Short Form-36 (SF-36), Subjective Cognitive Impairment Rating (SCIR) and

CPAP acceptance visual analogue scale. In addition, a neurocognitive test battery (Continuous Performance Test, Paced Auditory Serial Addition Test, Wechsler Memory Scale-Third Edition, Wechsler Intelligence Scale-Third Edition short form, Wisconsin Card Sorting Test, Purdue Pegboard Test, Trial A and Trial B and Stroop Test.) was administered.
Results: A stepwise multiple regression analysis was conducted. The variables included were derived from the following measures: sleep parameters and apnea indices from PSG record, subjective sleepiness score on the ESS, quality of life variables from the SF-36, subjective measures of cognitive impairment on the SCIRS and objective measures of neurocognitive performances. The results revealed that REM% (B=-.154, t=-1.868, P=.08), ESS (B=.603, t=2.737, P=.015) and total sleep time (B=-.0286, t=-2.450, P=.026) were the three predictors that could explain 62.3% of the variation of self-rating CPAP acceptance (adjust R square =.623, F=6.005, P<.05). The rest of the measures were all excluded by the model.
Conclusion: REM%, total sleep time and subjective sleepiness were found to be the most robust predictors of CPAP acceptance. Subjective ratings on cognitive impairments, quality of life, objective measures of neurocognitive performance, as well as indices of OSA severity (e.g., RDI,desaturation index) showed no influence on CPAP acceptance. Patients acceptance of CPAP may be improved if the clinicians can enhance their awareness of the impacts of OSA on their level of sleepiness and quality and quantity of sleep.

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Association between Alcohol Intake and Sleep-Related Oxygen Desaturation in the Community-Dwelling Japanese Men

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Introduction: There is few epidemiological data on the relation between habitual alcohol consumption and arterial oxygen desaturation during sleep.
Methods: We investigated association between alcohol consumption assessed by interview and arterial oxygen desaturation in 1422 men aged 40-69 years who participated in cardiovascular disease prevention survey carried out in three Japanese communities in 2001-2003. We performed nocturnal home pulse-oximetry by using PULSOX-3Si (Minolta) for monitoring oxygen saturation during sleep. We divided the subjects into five groups according to their daily ethanol intake levels; never (277 men), past (111 men), light (<0.5g/kg/day, 551 men), moderate (0.5-0.9g/kg/day, 393 men) and heavy (>=1.0g/kg/day, 90 men). The oxygen desaturation index (ODI) was defined as the number of events per hour of recording time in which blood oxygen fell by >=4%, and ODI>=5 was regarded as sleep disordered breathing (SDB).
Results: The mean log-transformed ODI was positively associated with alcohol consumption after adjustment for age and body mass index (BMI) (p=0.003, ANCOVA). The odds ratio of ODI>=5 among heavy drinkers compared to never drinkers was 3.35 (95%CI: 1.02-11.0). This trend was primarily observed among mean with lower BMI (<23.9kg/m2, below the median); the respective odds ratio was 3.86(1.53-9.73).
Conclusion: Alcohol consumption is associated with the severity of SDB in the community-dwelling Japanese men, particularly lean men.

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Measuring The Instability Of Upper Airway Resistance In Sleep Apnea

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Introduction: Although the severity of sleep disordered breathing (SDB) is often evaluated by counting and indexing apneas and hypopneas, the definitions are not uniform. In addition, SDB is a disorder of functional airway instability and there is increasing doubt about RDI as a reliable indicator of the severity of SDB. An obstruction in the upper airway causes the respiratory movements to be out of phase or asynchronous. As the increase in upper airway resistance is highly unstable during sleep, this phase relationship is susceptible to variability, whereby the extent of this variability may be dependent on the severity of the respiratory sleep disturbance. This paper describes a model (Respiratory Mechanics Instability or RMI), based on the variability in this phase relationship.
Methods: 139 Patients with Respiratory Disturbance Index (RDI) ranging from 0.0 to 107 were recorded with full polysomnography (REMbrandt system). Patients with RDI>5 were classified as SDB patients. Abdominal and rib cage effort were recorded with piezo sensors. The Respiratory Mechanics Instability (RMI) was calculated from the variance in the phase relationship between the 2 effort signals. The percent of time spent in RMI state (periods of instability of respiratory mechanics higher than baseline level) was called the RMI-index (RMI-I).
Results: The Respiratory Mechanics Instability Index was positively correlated with the RDI values (Spearman rho correlation: 0.67, p<.001). Using the criterion of an RDI>5 as SDB classification standard the percentage of agreement with RMI-I values was calculated. The number of False Negatives was only 2.9%. The number of True Positives and True Negatives were 67.1% and 10.7% respectively, whereas the number of False Positives was 19.3%. However, 50% of the patients with low RDI, but with higher RMI-I were UARS patients. The RDI could not detect these patients, while the RMI-I did. When the number of correctly diagnosed patients were corrected accordingly, the number of False Positives was decreased to 10% and the number of True Positives was increased to 76.4%, resulting in 87.1% correctly classified patients. The sensitivity of the RMI-I to detect sleep apnea patients was 0.96% and the specificity was 0.52%. The Receiver Operating Characteristic (ROC) curve was determined to evaluate the classification of SDB patients (classified with the RDI) by RMI-I. The area under the curve (0.881) was significantly different from chance (p<0.001). The trade-off between the optimal levels of sensitivity and specificity of the RMI index yielded a sensitivity of 0.82 and a specificity of 0.80.
Conclusion: The modeling of thoracic and abdominal interaction is a promising method to quantify respiratory disturbance during sleep. The variability in the phase relation between thorax and abdomen is a reliable indication of airway instability. The calculation of this phase relationship results in a phase value per second, so that the RMI has a higher time resolution than the RDI.

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Is the Epworth Sleepiness Scale (ESS) a too Simplistic Tool in the Measurement of Excessive Sleepiness for Obstructive Sleep Apnoea?

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Introduction: The Epworth Sleepiness Scale© (ESS)1 is a simplistic questionnaire routinely used as a tool in Sleep clinics across the UK to

measure excessive sleepiness associated with Obstructive Sleep Apnoea (OSA). Subjects customarily complete an ESS pre therapy and continue to fill in ESS during therapy to assess the therapeutic benefit of Positive Airway Pressure (PAP) treatment. This measurement, in conjunction with clock hours (i.e. time of PAP device on) data, is often used to indicate the benefit of PAP which many Sleep professionals rely on when verifying successful treatment to organisations such as the Driver and Vehicle Licensing Authority (DVLA). The aim of our study was to retrospectively analyse the Epworth Sleepiness Scale (ESS) with the Functional Outcomes of Sleep Questionnaire©(FOSQ) 2, in subjects receiving PAP therapy to see if there was any difference in excessive sleepiness scores when completing a simplistic questionnaire (ESS) with a more complex one (FOSQ).
Methods: ESS and FOSQ data was retrieved and analysed from 100 subjects pre PAP therapy and at day 30 whilst on PAP therapy. Subjects recorded ESS by a paper questionnaire and FOSQ was recorded on an Encore Pro® SmartCard™ by completing the built-in questionnaire in a Respironics® REMstar® device. An abnormal ESS was determined by a score of 11 or greater and an abnormal FOSQ score was classed as a value below 16.33.
Results: Using a Chi-square 2 by 2 table (continuity correction) ESS identified 92 subjects with excessive daytime sleepiness (EDS), and FOSQ identified 84 subjects with EDS at baseline. On treatment, ESS only identified 17 subjects with excessive sleepiness compared with 28 subjects identified by FOSQ. No significant difference was shown between ESS and FOSQ at baseline (p=0.065). A significant difference was shown between ESS and FOSQ for subjects whilst on treatment, with FOSQ identifying a greater number of sleepy subjects. ($p < 0.01$).
Conclusion: This study raises issues as to the reliability of simplistic tools in the measurement of excessive sleepiness whilst on therapy. With ESS being the usual recorded measurements, by Sleep professionals for assessing therapeutic benefit, and is sufficiently simplistic to be potentially open to manipulation, this study raises doubts as to the validity of simplistic questionnaires for verifying therapeutic benefit.

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Does Positive Airway Pressure Therapy Provide a Symptomatic Benefit at Low Levels of Compliance?

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Introduction: In the United Kingdom, positive airways pressure (PAP) therapy is primarily prescribed to treat the excessive daytime sleepiness (EDS) associated with Obstructive Sleep Apnoea (OSA). Current criteria of regular use already reported in literature suggests that PAP usage of 4 hours per night, 70% of nights is required to receive a symptomatic benefit, although anecdotal evidence suggests that subjects who struggle to achieve these levels still subjectively report a positive benefit from PAP therapy. Therefore we aimed to determine whether subjects with PAP compliance levels of < 4 hours per night all days, still obtain significant symptomatic benefit.
Methods: Epworth Sleepiness Scores (ESS) were retrospectively analysed from 89 subjects (who had been positively diagnosed with OSA) pre and during PAP therapy (minimum time on therapy = 8 weeks) enrolled on a therapeutic programme. These subjects were then stratified according to their compliance levels (<3, 3-3.9, 4-4.9, 5-5.9, 6-6.9, 7-7.9 hours per night all days) and the change in ESS from baseline was calculated for each group.
Results: The mean duration of PAP therapy for the group was 24 weeks. There was a significant reduction in ESS scores from baseline in all of the compliance groups (<3 hours per night all days, = -5.1 ±0.9; 3-3.9 = -6.1±1.1; 4-4.9 = -6.1±0.9; 5-5.9 = -7.8±1.1; 6-6.9 = -9.1±1.2; 7-7.9 = -12.8±1.8, $p<0.01$ for all groups on paired t-test analysis). In this group, a highly significant reduction in ESS values was shown as compliance levels increased. ($p < 0.001$ using a one way ANOVA).
Conclusion: For this group, PAP therapy provides a subjective symptomatic benefit in all subjects with OSA, even when compliance levels are below the recommended therapeutic compliance level (< 4 hours per night, 70% nights). However, on analysis of data within this group, it is also suggested that by achieving higher compliance levels, greater reductions can be achieved in subjective EDS measurements.

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Sleep And Vascular Disease In The Caerphilly Cohort Of Older Men

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Introduction: Sleep disorders are associated with vascular disease which leads to morbidity and mortality but it is not clear if this is relationship is causal. Many epidemiological studies of sleep disorders have assessed OSA. A prospective analysis from the Wisconsin Sleep Cohort showed that OSA predated hypertension and a dose response relationship was observed. Studies of OSA suggest a link with myocardial infarction but the only prospective data supporting this link is from longitudinal studies of snoring. Studies link snoring and OSA with stroke but the causality remains unclear. One prospective cohort study of a sleep clinic population suggests that OSA is an independent risk factor for the development of a stroke. Given the high prevalence of some of the sleep disorders and the range of severity it is important to understand the morbidity and mortality relationships. The aim of this study is to test the hypothesis that sleep disorders are relevant to the risk of ischaemic heart disease and ischaemic stroke in older men.
Methods: A representative group of 1,986 adult males age 65 to 79 years from Caerphilly in South West Wales completed the Wisconsin sleep questionnaire that asks about symptoms of sleepiness, insomnia, restless legs, snoring and episodes of apnoea in 1992. Symptoms were grouped into never, occasional and frequent. Men with a previous history of myocardial infarction or stroke were excluded. Outcomes considered are incident ischaemic heart disease and ischaemic stroke during the seven to ten years after submission of the questionnaire.
Results: 32% of the men reported frequent daytime sleepiness. 36% of men reported frequent snoring, 19 % reported frequent episodes of apnoea that indicates the possibility of underlying OSA, 12% of men reported frequent symptoms of insomnia and 23% reported the presence of restless legs. Over the period of the study 298 men had a vascular event. The predictive power of sleep disturbance for incident heart disease by insomnia is OR 1.63 (95% confidence interval 1.06-2.51, $p<0.027$) and by daytime sleepiness is OR 1.47 (1.05-2.07, $p< 0.026$). The predictive power of sleep disturbance for incident ischaemic stroke by symptoms of OSA is OR 1.79 (1.14-2.82, $p<0.012$). The relative odds of an event of either ischaemic heart disease or ischaemic stroke in men who reported any symptoms of frequent sleep disturbance was OR 1.49 (1.14-1.95,$p<0.004$).
Conclusion: Sleep disorders are relevant to the risk of vascular disease in older men. This is the first study using prospective incidence data from a population sample to show that symptoms of OSA precede the development of stroke. The presence of frequent symptoms indicating daytime sleepiness or insomnia was significantly predictive of the occurrence of a myocardial infarction and the presence of frequent symptoms of OSA was significantly predictive of a stroke. It is of great importance to establish public health initiatives for reducing risk factors in sleep disorders and vascular diseases and to achieve sufficient clinical resources to identify cases and provide effective treatment whilst monitoring vas-

cular outcomes.

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Are Sleep-Related Breathing Disorder In Hemodialysis Patients Mildest On The Dialysis Day?

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Introduction: Sleep-related breathing disorder (SRBD) are highly prevalent in hemodialysis patients. Jean et al hypothesized that inadequate dialysis buffer might play as a causative factor for the occurrence of SRBD in the patients with end-stage renal disease (ESRD). On the other hand, some reports showed SRBD in ESRD patients was resolved after kidney transplantation or intensive nocturnal hemodialysis. However, detailed mechanisms remain to be elucidated. In order to clarify this issue, changes in SRBD severity through dialysis schedule and its relation to background factors relevant to dialysis and/or uremia were investigated in the patients with ESRD.

Methods: Six male patients (age: 67.8±6.3, dialysis history: 6.4±4.7 years) consented to take part in this study. All these patients showed apnea-hypopnea index (AHI) ≥ 20 on the night after hemodialysis (mean±SD; 61.4±26.3). They underwent hemodialysis at three-days intervals, and all the hemodialysis sessions were performed for four hours in the daytime. We carried out polysomnographic (PSG) recordings on four consecutive nights from one hemodyalysis day through the next hemodialysis day. We also analyzed changes in body weight, uremia material and arterial blood gas findings between just before and after.

Results: Although nocturnal lowering grade of oxygen saturation did not differ among four consecutive PSG, AHI was statistically different among first, second, third and fourth day (the next hemodialysis day). AHI was 51.1±30.5, 61.8±26.0, 64.9±33.5, and 52.1±33.5, respectively. The averaged AHI on the nights just after daytime dialysis were significantly milder than those on days without dialysis (first and fourth day vs. second and third day; 55.3±29.9 vs. 67.6±27.0, p=0.0007). Regarding sleep architecture, sleep efficiency on days with dialysis was significantly higher than that on days without dialysis (73.4±14.0 vs. 68.5±14.5, p=0.009). Both the percentage of stage 1 and stage REM were different between the days with and without dialysis (stage I: 42.6±18.3 vs. 57.6±17.4, p=0.0008; stage REM: 18.7±7.9 vs. 13.7±6.5, p=0.0052, respectively). Body weight difference was statistical but small (BMI: 20.7±3.0 vs. 21.5±2.8,p=0.001) through these four days. Metabolic acidosis on blood gas finding was observed just before dialysis, and improved after dialysis (PH: 7.372±0.022 vs. 7.458±0.010, p=0.002; PaCO2: 38.2±4.0 vs. 36.0±3.4, n.s.; HCO3: 21.8±2.8 vs. 25.3±2.4, p=0.0043; BE: -3.0±2.8 vs. 2.0±2.2, p=0.0012, respectively). The uremic materials were significantly decreased after dialysis (BUN: 74.3±13.9 vs. 24.7±5.0, p=0.0001; creatinine: 11.1±2.1 vs. 4.4±1.1, p=0.0001).

Conclusion: It was revealed that SRBD in dialysis patients significantly fluctuates with dialysis schedule, and that the disorder is worse on the day without hemodialysisis than the day with hemodialysis. Increase of stage REM, in which respiratory disorder tends to become worse, may not be negligible. Among dialysis and/or uremia factors, excess in body fluid, manifested as the increase in body weight, seemed to be too small to aggravate the narrowing of upper airway on the day without hemodialysis, and metabolic acidosis, which usually stimulates respiratory drive, was not thought to contribute to the worsening of the disorder. Thus, cumulative uremia material may have larger influence on the worsening of SRBD than the other factors.

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Tongue Base Suspension With The REPOSE TM System In The Surgical Management Of Obstructive Sleep Apnea

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Introduction: About 50% of patients with OSA present hypo-pharyngeal collapse. Genioglossal advancement with hyoid suspension is the most popular procedure used for the treatment of the hypo-pharyngeal obstruction. Recently De Rowe et al presented a new minimally invasive technique for tongue base suspension in the treatment of hypo-pharyngeal collapse. This technique uses a titanium screw and a permanent suture to anchor the tongue base to the inner mandibular cortex. The aim of this study is to evaluate the effectiveness of this minimally invasive procedure in the management of OSA.

Methods: Fifteen male patients underwent UPPP in conjunction with tongue base suspension with Kit ReposeTM bone screw system from January 2000 to December 2001. Preoperative evaluation included: clinical history, physical examination, fibre-optic nasopharyngoscopy with Muller manoeuvre, lateral cephalometric analysis, Epworth sleepiness scale (Ess) and nocturnal sleep study with a cardio respiratory monitor (Embletta FLAGA, Iceland). The following variables were recorded for sleep study: 1) airflow (nasal cannula pressure trasducer); 2) thoracic and abdominal movements; 3) snoring sound; 4) arterial oxygen saturation; 5) heart rate; 6) body position; 7) body movements. Automatic analysis of nocturnal recordings was performed on sleep period referred by patients (sleep diary) and reviewed manually by certified sleep specialist. The UPPP was performed using the Simmons technique; the tongue base suspension was performed as described by De Rowe. Endoscopic and cephalometric follow-up were performed one month after surgery. Postoperative sleep study was obtained 4 to 6 months after surgery.

Results: The mean age of the patients was 50.5 (range 36-66), with a mean BMI of 28.3 (range 22.6-34.3). The group had moderate/severe OSA with a mean RDI of 44.5 (range 23-63) and lowest O2 desaturation of 79%. The mean Ess value was 11.2 (range 7-14). All patients presented type II upper airway obstruction according to Fujita classification (oropharyngeal/hypopharyngeal narrowing), as demonstrated by Muller manoeuvre and cephalometric analysis. No case of postoperative complication was noted. Mean hospital stay was 3.4 days (range 2-5). At one month no patient referred speech or swallowing difficulties. In twelve patients (80%) both snoring and sleepiness improved (mean Ess=6.6). The mean postoperative RDI was 24.2, which is a reduction of 45%. The mean lowest O2 desaturation increased from 79% to 84.9%. The surgical cure rate was 40% (6 patients).

Conclusion: This study demonstrates that the role of the tongue base suspension technique in the surgical management of OSA is somewhat limited. Even if this procedure is miniinvasive and easy to perform the results are not different from those obtained with oropharyngeal surgery alone and worse with respect to those reported with genioglossal advancement in association with hyoid suspension. The surgical solution of the retrolingual obstruction is given either by maxillomandibular

advancement or by the resection of the tongue base: even if highly invasive, these are definitely effective surgical procedures.

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Comparison Of Mortality Risk Between Men And Women Using CPAP For Obstructive Sleep Apnea

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Introduction: There is evidence that women with obstructive sleep apnea (OSA) have a greater mortality risk than men. We have studied a sample of OSA patients diagnosed and regularly monitored at our Sleep Center to assess whether women have a greater mortality risk independent of age, severity of OSA and concordance with continuous positive airways pressure (CPAP).
Methods: The hospital notes of patients with: OSA; not due to a neuromuscular disorder; an overnight ≥ 4% oxygen desaturation index (DI) of ≥ 5 per hour; started on CPAP between July 1995 and June 1998, were reviewed between August and December 2003. Patients have been monitored at least annually unless we withdrew or they discontinued CPAP, or they transferred to another hospital. Data was collected regarding: gender, date of birth, date CPAP was started, pre-treatment Epworth Sleepiness Scale (ESS) score, DI, mean and minimum oxygen saturation (SpO2) and BMI. The hours of CPAP use for living patients and those using CPAP up to their death, under our follow-up were recorded. The mortality status of the remaining patients was determined using the National Health Service tracking system, which records deaths of all UK patients accurate to within 2 weeks. Non-parametric tests were used to compare baseline ESS and oximetry results, age and BMI when CPAP was started, CPAP uptake and average nightly hours of use between men and women. Multivariate Cox's Proportional Hazards Regression was used to identify if gender, age when started CPAP or baseline oximetry results had independent associations with mortality risk using the likelihood ratio test. BMI and ESS were not entered into the model due to missing data.
Results: 340 patients (86% men) met the inclusion criteria. Comparisons between men and women showed that before treatment the women had a higher BMI (n = 314; median = 37.1 vs. 32.1; p = 0.010) while men had a higher DI (median = 19.0 vs. 14.0; p = 0.019). 30 (8.8%) patients had died (21.3% of women and 6.8% of men). Mortality was independently associated with female gender (hazard ratio (HR) = 3.018; p = 0.005), age when starting CPAP (HR = 1.074; p < 0.001) and minimum SpO2 (HR = 0.953; p < 0.001) but not with mean SpO2 or DI. There was no significant sex difference in the median nightly hours of use of CPAP of living patients or those who died under our follow-up (men = 6.9; women = 7.1). There were proportionally fewer women still under our care (55% vs. 71%; p = 0.042) but we cannot state how many had discontinued CPAP therapy.
Conclusion: Our results demonstrate that women with OSA started on CPAP treatment are 3 times more likely to die at a given time compared to men independent of age when treatment was started or severity of OSA. This is not explained by lower treatment concordance in CPAP users but poorer uptake may be a factor. Greater obesity in the women compared to the men may explain some of the increased risk.

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Sleep-Related Respiratory Disorders In Patients With Gastroesophageal Reflux Symptoms. A Clinical Populational Study

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Introduction: The prevalence of gastroesophageal reflux disorder (GERD) in the adult population is 5%, similar to the prevalence of sleep related breathing disorders. The relationship between GERD, BMI and breathing disorders is still unclear. The aim of this study is to assess the frequency of GERD symptoms in individuals referred to a Sleep Clinic, and to evaluate sleep in this group of patients.
Methods: Outpatients of the Sleep Clinic - UNIFESP-Brazil, referred to PSG study including EEG, EMG, EOG, ECG, respiratory parameters, and oxymetry. during 2002 and 2003 (N = 5138) were evaluated. Heartburn and regurgitation were assessed through a questionnaire. Patients who had one of the two mentioned symptoms, at least twice a week, were considered as GERD-symptom positive (GROUP 1) and GERD-symptom negative (GROUP 2) otherwise.
Results: Heartburn and/or regurgitation was reported by 842 (16,3 %) of the patients. The female:male ratio was 1.2:1.0 (GROUP 1) and 1.6:1.0 (GROUP 2); p = 0.004. Age distribution was 47.4 +/- 12.4 and 45.9 +/- 13.5; respectively; p = 0.004. In GROUP 1, BMI was significantly higher than in GROUP 2 (29.4 +/- 6.9 e 28.1 +/- 6.7 respectively; p < 0.001), with BMI>30 in 33,8% (GROUP 1), and 24.4% (GROUP 2), p<0.001. Regarding Epworth Scale, scores in GROUP 1 (n=828) were significantly higher than in GROUP 2 (n=4058): 11.2 +/- 6.3 and 9.8 +/- 5.6, respectively, p< 0.001. Evidence of daytime somnolence (Epworth > 10) were observed in 52.3% of GROUP 1 patients and 43,5% in GROUP 2, p< 0,001. The median value of apnea-hypopnea index (AHI) was higher in GROUP 1 than in GROUP 2 (17,8 and 6.8 /h, respectively, p = 0.004). AHI > 30 /h were verified in 20% of GROUP 1 subjects and in 16.3% in GROUP 2, p = 0.006. Minimal oxi-hemoglobin saturation was lower in GROUP 1 than in GROUP 2, 82.7 +/- 9.4 e 84.4 +/- 8.6 %; respectively, p< 0.001. Values below 90% were detected in 7.3% of GROUP 1 subjects, while only in 69.6% in GROUP 2, p< 0.001.
Conclusion: This study evidences the association between gastroesophageal reflux symptoms and sleep. Oxi-hemoglobin dessaturation during sleep observed in the GERD group of subjects were related, not only to obesity (BMI > 30), but also to respiratory events, such as AHI >30/h. Daytime somnolence was also related to gastroesophageal reflux symptoms. The presence of gastroesophageal reflux symptoms in subjects with complaints of sleep disorder can worsen the sleep disturbances.

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Prevalence Of Self-Reported Sleepiness In Patients With Cardiac Permanent Pacemaker

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Introduction: Heart disease and cardiac arrhythmias are prevalent in patients with sleep disordered breathing. However, prevalence of sleep complaints in patient with cardiac permanent pacemaker (PPM) is not known. We report here the results of a sleep survey performed in patients with PPM.

Methods: We identified patients with PPM using the Houston VA Medical Center electronic database. A brief sleep symptoms questionnaire and the Epworth sleepiness scale were mailed to the patients. A self-stamped return envelop was included with the questionnaires. We used STATA software to analyze the data. To determine the association between sleepiness (measured with ESS) and other parameters, we performed a stepwise multiple regression analysis.
Results: We identified 404 subjects with PPM. Of these 243 (60%) completed and returned the questionnaires. The responders had the following demographics: mean age 73, mean height 68 inches, mean body mass index (BMI) of 27.7, and mean ejection fraction of 45%. This sample reported the following sleep problems: ESS > 12 in 39%, falling asleep while driving in 12%, snoring in 51%, waking up gasping for air in 28%, witnessed cessation of breathing in 26%, restless sleep in 55%, unrefreshing sleep in 152 63%, insomnia in 50%, and unusual behavior during sleep suggesting parasomnia in 33%. There was no significant difference in demographic variables for ESS below and above 12. In multiple regression analysis, age (p = 0.05) and bradycardia as PPM indication (p = 0.007) correlated with sleepiness.
Conclusion: Excessive sleepiness and sleep complaints are prevalent in patients with PPM. Bradycardia as PPM indication was associated with the excessive daytime sleepiness. Further work is needed to investigate this association and its underlying mechanisms.

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Association of Nocturnal Arrhythmias with Sleep-Disordered Breathing: the Sleep Heart Health Study

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Introduction: The relationship between nocturnal arrhythmias and sleep-disordered breathing (SDB) appears to have sound basis on the grounds of biologic plausibility. The pathophysiology of SDB including recurrent intermittent hypoxia, sympathetic nervous system surges, and activation of inflammatory pathways provides the proper milieu for the development of arrhythmias. Despite this, the literature currently is conflicting regarding evidence of increased presence of nocturnal arrhythmias in the setting of SDB. We postulate that the prevalence of nocturnal cardiac arrhythmias (pathologic and non-pathologic) is higher among subjects with SDB (Respiratory Disturbance Index, RDI>30) versus those without SDB (RDI<5).
Methods: The design was a nested group frequency-matched exposed-unexposed study of data collected during the Sleep Heart Health Study-2 (SHHS-2) examination. Subjects underwent in-home unattended 12–channel polysomnograms (PSGs) and completed standardized questionnaires. The RDIs were based on scoring respiratory events with a 3% oxygen desaturation or greater. The exposed subjects (SDB: n= 250) were frequency-matched to an unexposed group (non-SDB: n=368) with respect to age (± 2 years), gender, ethnicity, and body mass index (BMI, ± 2kg/m2). Lead I electrocardiogram (EKG) data collected at a 250 Hz sampling rate with PSG was analyzed using software specific for the interpretation of EKG data collected during PSG (Somté®, CompuMedics®, Abbotsford, AU), and then manually edited in an intensive fashion while blinded to the RDI. The occurrence of supraventricular, ventricular, and conduction abnormalities were coded.
Results: Mean (±SD) of age, BMI, and RDI were 68.4±9.1 years, 28.5± 4.2 kg/m2, 2.7±1.4 events/hr in the unexposed subjects compared to 70.3±9.9 years, 30.1± 4.5, and 45.1 in the exposed. Respectively, 49% and 50% of the unexposed and exposed subjects were males. A high frequency of premature ventricular contractions was observed in the cohort (79%), with no differences according to SDB status. Atrial fibrillation (AF), complex ventricular ectopy (CVE, defined as bigeminy, trigeminy, quadrigeminy or ventricular triplets), and non-sustained ventricular tachycardia (NSVT) were more common in the exposed than non-exposed: 4.8% vs. 0.8%, p=. 002, for AF; 22.0% vs. 13.9%, p=. 01 for CVE; 6.1% vs. 1.9%, p=. 008, for NSVT. The age, gender, and BMI-adjusted SDB Odds Ratio (95%CI) were: for AF: 4.5 (1.2,17.0); for CVE or NSVT: 1.8 (1.2, 2.8); and for AF or NSVT: 3.7 (1.7, 8.0). No significant group differences were observed for conduction delays or less severe arrhythmias.
Conclusion: Although the overall prevalence of certain nocturnal arrhythmias is low, individuals with moderate to severe SDB had a 2-4 fold higher odds of pathologic arrhythmias than those without SDB. This association may be mediated by underlying structural cardiac disease as well as associated risk factors, and the extent to which this effect occurs cannot be inferred. These results have direct clinical implications, and emphasize the importance of EKG screening of PSG in the sleep laboratory.

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Circulatory Response in Sleep Apnea Patients and Normal Controls During Sleep

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Introduction: Obstructive sleep apnea (OSA) impairs breathing and leads to repetitive hypoxia and arousals. OSA is associated with hypertension, heart failure arrhythmia and death. Apneic episodes are presumed to cause hemodynamic alterations however few studies have documented these changes in different stages of sleep. The aim of the study was to assess the circulatory response to various sleep stages in patients with OSA and normal controls using impedance cariography (ICG).
Methods: We studied 9 OSA patients (AHI = 60/hr) and 3 controls (AHI = 8/hr). Hemodynamic monitoring was done non-invasively during entire overnight polysomnography using impedance cardiography by BioZ
Results: The cardiac output and cardiac index decreased during sleep in both OSA patients and controls. The cardiac output decreased by 22%, cardiac index by 24% and systemic vascular resistance (SVR) increased by 15% in OSA patients compared to a decrease of 14% in both cardiac output and index and a decrease in 4% in SVR in control patients. The p values were statistically significant at 0.00009, 0.0008, and 0.0002 respectively.
Conclusion: Significant hemodynamic changes occurring during sleep are much more pronounced in OSA patients as compared to controls. Possible explanations such as increased intrathoracic pressure during apneic episodes limiting cardiac contractility and stroke volume and/or decreased pulmonary vascular capacitance remain to be explored.

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Effects of Bi-Level Therapy in Heart Failure Patients with Cheyne Stokes Respiration

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Introduction: In patients with a reduced Left Ventricular Ejection Fraction (LVEF) and sleep disordered breathing there is an increased mortality risk. The aim of this study was to analyze the effects of a bi-level therapy on the LVEF, respiratory parameters during sleep, sleep structure and clinical complaints.
Methods: We included 34 men and 3 women with a mean age of 58.9 ± 10.4 years and a mean BMI of 28.0 ± 3.9 kg/m2. In all patients Cheyne Stokes Respiration (CSR) was diagnosed by polysomnography and described by the Central Apnea Index (CAI), the Periodic breathing Index(PBI) and the CSR Index (CSRI = CAI+PBI). The LVEF was determined by echography. Following the application of bi-level-therapy patients underwent polysomnography and cardiac investigation 6 weeks after.
Results: 30 out of 37 patients could be investigated 6 weeks after bi-level-therapy initiation. The LVEF increased from 25 ± 8.5 % to 29.1 ± 9.8 % ($p<0.005$). The CAI decreased from 15.3 ± 16.3 /h to 2.1 ± 4.6 ($p<0.0001$), the PBI decreased from 16.9 ± 9.9 /h to 11.5 ± 12.2 /h ($p<0.002$), the CSR Index (CSRI) decreased from 32.3 ± 16.2 /h to 13.6 ± 13.4 /h ($p<0.0001$) and the Oxygen Desaturation Index (ODI) decreased from 30.1 ± 25.9 /h to 13.6 ± 13 /h ($p<0.001$). Sleep macrostructure did not change, whereby the respiratory related arousal decreased ($p<0.0001$) and movement arousal increased ($p<0.03$). During therapy the ESS decreased from 10.2 ± 4.2 to 8.4 ± 3.6 ($p<0.05$). There were no changes in lung function test.
Conclusion: In patients with reduced LVEF the bi-level therapy is effective with regard to treatment of sleep related breathing, improvement of LVEF, and slight reduction of daytime sleepiness.

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A Model Of Upper Airway Resistance Syndrome In The Monkey

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Introduction: Upper airway resistance syndrome is characterized by an increasing effort for breathing during sleep inducing mechanical stimulation of the upper airway. Up to now, few chronic animal models mimic nocturnal breathing disorders and we therefore considered creating a new animal model to reproduce the upper airway resistance syndrome.
Methods: Animals: We used 3 female cynomolgus monkeys (Macaca fascicularis, Shared Animal Health, Beijing, PR of China) supervised by veterinarians skilled in the healthcare and maintenance of non-human primates. Sleep recordings. Monkeys were equipped with surface electrodes taped on the skull, face and chest that allow monitoring of the following variables: EEG(C3/A2 - C4/A1), electro-oculogram (EOG), chin electromyogram (EMG), one ECG derivation, nasal pressure and oral flow (thermistor), snoring, thoracic and abdominal respiratory movements and oxygen saturation. Polysomnographic recordings were performed from 8 pm until 6 am. Model design: Monkeys received intra dermal injections of liquid collagen in the upper airway and polysomnographic recordings were performed regularly to control the impact of injections on esophageal pressure and EEG during sleep.
Results: Impact of collagen injections on nocturnal breathing events: Before injection, animals presented a mean of 4.8 +- 2 hypopneas per hour of sleep. The mean duration of theses hypopneas was 11.7 +- 3.2 minutes. After injection (3months), there was a significant increase of breathing events with a mean of 27.9 +- 19.7 hypopneas per hour of sleep (Kruskall Wallis, $p < 0.04$). The mean duration of theses hypopneas was 15.1 +- 8.6 minutes. Impact of collagen injections on sleep architecture: During the baseline nights, animals slept 122 +- 87 minutes. Stage I represented 53 +- 39 % of the total sleep time, Stage II represented 43 +- 38 % of the total sleep time, Rem sleep represented 2 +- 3.2 3.7 % and Stage III represented 2 +- 3.2 %. 3 months after injection, The percentage of stage I significantly increased (kruskal wallis, p=O.O3). Percentages of stage II and REM sleep were significantly decreased (kruskal wallis, p=O.O3, p=O.O37). There was a significant reduction of duration of stage II (kruskal wallis, p=O.O2) and REM sleep (kruskal wallis, p=O.O3). There was a significant relationship between the number of hypopneas > to 20 seconds and the total sleep time (Pearson coefficient, $R = 0.652$, $p < 0.03$) as well as the duration of stage I (Pearson coefficient, $R = 0.808$, $p < 0.03$). There also was a significant correlation between the number of hypopneas > to 30 seconds (Pearson coefficient, $R = 0.671$, $p < 0.02$) and the duration of stage I.
Conclusion: Compared to healthy monkeys, our animal model present significant nocturnal breathing events and a sleep architecture comparable to the one seen in the upper airway resistance syndrome. Further studies need to be performed to confirm on a larger sample the impact of breathing events on daytime vigilance and cardiovascular factors.

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Predictors of Asymptomatic Sleep Apnea-Hypopnea in Patients Treated with Continuous Positive Airway Pressure

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Introduction: Patients with obstructive sleep apnea syndrome (OSAS) once treated with continuous positive airway pressure (CPAP) often feel symptomatically improved. Polysomnography of consecutive patients who denied snoring or daytime somnolence while using CPAP has found that some patients still had significant OSA. We sought pre-test clinical characteristics that would help to identify this small group of patients.
Methods: We studied 37 consecutive patients treated with single-pressure CPAP for at least 3 months who denied their previous symptoms of OSAS. All had undergone CPAP titrations which guided the CPAP prescriptions. All subjects completed questionnaires then underwent polysomnography with EEG and a pneumotachometer at home (Alice 4, Respironics) while using their usual CPAP. Hypopneas were scored if at least 4% oximetry desaturation was seen. Patients were considered to have persistent OSA if they still had an apnea-hypopnea index (AHI) of 10 or more.
Results: Five of 37 (14%) had persistent OSA. No patients had predominantly central apnea. None had a current Epworth score over 8. Mean current Epworth sleepiness score of those with persistent OSA was 5.0 (3.7) similar to those with no OSA (AHI < 5) ($p = 0.45$). When comparing those with persistent OSA to those with no OSA, there was no difference in age, gender, time since diagnosis, snoring, current weight, change in weight, quality of life, vitality, or mood (all $p > 0.10$). Mean AHI at diagnosis of those with persistent OSA was higher 114 (66)

vs. 55 (51) per hour (p = 0.029), current CPAP level was higher 11.2 (2.8) vs. 8.1 (2.2) cm H2O (p = 0.008). Those with persistent OSA more often complained of symptoms of air leak related to CPAP.
Conclusion: Persistent OSA is frequent in asymptomatic patients who are treated with CPAP for OSAS. Periodic oximetry and CPAP readjustment may be warranted in selected asymptomatic patients treated with CPAP for OSAS who have higher prescribed pressures and symptoms of air leak.

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Tongue Base Reduction with hyoepiglottoplasty in severe Obstructive Sleep Apnea: experience in 8 cases

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Introduction: The surgical correction of the retro-lingual collapse in OSA patients is still lacking in a consensus opinion. Maxillomandibular advancement is the most common surgical technique employed in severe OSA when craniofacial abnormalities are present. Tongue base reduction with hyoepiglottoplasty (TBRHE) described by Chabolle in 1999, is a one-phase invasive surgical procedure for the correction of the morphologic and positional abnormalities of the hyolingual complex. Only ten cases are described in the literature with TBRHE.
Methods: Eight patients with severe OSA and moderate obesity (mean RDI 55.1 ; mean BMI 30.6) who failed to tolerate nasal C-PAP therapy were treated with TBRHE in conjunction with UPPP. Patients were selected on the basis of severe hypo-pharyngeal obstruction in the absence of cranium-facial abnormalities. Preoperative evaluation included: clinical history, physical examination, fibre-optic nasopharyngoscopy with Muller manoeuvre, lateral cephalometric analysis, Epworth sleepiness scale (Ess) and nocturnal sleep study with a cardio-respiratory monitor (Embletta FLAGA, Iceland). The following variables were recorded: 1) airflow (nasal cannula pressure transducer); 2) thoracic and abdominal movements; 3) snoring sound; 4) arterial oxygen saturation; 5) heart rate; 6) body position; 7) body movements. Automatic analysis of nocturnal recordings was performed on sleep period referred by patient (sleep diary) and reviewed manually by sleep specialist. The surgical technique was carried out by a cervical approach; after the identification of the lingual artery and of the hypoglossal nerve a subtotal tongue base resection was performed. The procedure was completed with the hyoid bone suspension to the lower border of the mandible and temporary tracheotomy. One month after surgery endoscopic and clinical evaluation was performed, moreover the swallowing function was studied by video fluoroscopy. Postoperative sleep study was obtained 4 to 6 months after surgery.
Results: Patients mean hospital stay was 15 days (range 12-19). No postoperative complications occurred and tracheotomy was removed before hospital discharge. At one-month follow-up we did not observe any abnormalities as regards to lingual mobility, speech and swallowing. Postoperative sleep study demonstrated significant improvement of respiratory parameters in all patients: mean RDI decreased from 51.3 to 9.7, mean low SaO2 increased from 78% to 90.4%. All patients showed a 50% reduction of preoperative RDI and a postoperative RDI less than 20. Overall surgical success rate was 100%.
Conclusion: TBRHE permits a significant enlargement of the hypo-pharyngeal airway without injury for the lingual function. Although it is an invasive technique, it allows to achieve good results in the treatment of patients with severe OSA and moderate obesity when abnormalities of the hyolingual complex is the main cause of obstruction . The key for success is the identification of the site of obstruction in hypo-pharyngeal airway in the absence of cranium-facial abnormalities. Our results suggest that TBRHE, when indicated, can be a valid treatment alternative in severe OSA patients who did not tolerate N-CPAP.

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Marked Decrease of Sleepiness in Patients with Sleep Apnea by Etanercept

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Introduction: Tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL-6) are elevated in obstructive sleep apnea (OSA) and in experimentally-induced sleepiness, and they are proposed as mediators of excessive daytime sleepiness in humans.
Methods: We tested the effects of etanercept, an FDA approved medication for the treatment of rheumatoid arthritis that neutralizes TNFα, in eight male, obese apneics who participated in a placebo-controlled, double-blind study during which nighttime polysomnography, multiple sleep latency test (MSLT), and plasma levels of IL-6, C-reactive protein, insulin, fasting blood sugar, and adiponectin were obtained.
Results: There was a significant and marked decrease of sleepiness by etanercept which increased sleep latency during MSLT by 3.1 + 1.0 min ($P < 0.05$) compared to placebo. Also, the number of apneas/hypopneas per hour was reduced significantly by the drug compared to placebo (52.8 + 9.1 vs. 44.3 + 10.3; difference -8.4 + 2.3; $P < 0.05$). Furthermore, IL-6 levels were significantly decreased after etanercept administration compared to placebo (1.9 + .4 vs. 3.8 + .9 pg/ml; $P < 0.05$). Insulin resistance indices were not affected by the drug.
Conclusion: Neutralizing TNFα activity is associated with a significant reduction of sleepiness in obese patients with OSA. This effect, which is about threefold higher compared to the reported effects of continuous positive airway pressure (CPAP) in patients with OSA (0.9 min vs. 3.1 min), suggests that pro-inflammatory cytokines contribute to the pathogenesis of OSA/sleepiness. Interventional studies attempting to correct these abnormalities will promote the understanding of the pathophysiologic mechanisms of sleepiness/OSA and will lead to more effective treatments of these highly prevalent and morbid disorders.

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Risk of Mortality associated with Sleep Disordered Breathing in a Population Sample

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Introduction: There have been several studies indicating that patients with sleep apnea are at increased risk for mortality.1-5 All of these studies to date have been based on clinical samples. The purpose of this study was to establish mortality rates associated with sleep disordered breathing in a general population sample.
Methods: This study is based on the followup of the Penn State Cohort that was initially evaluated in the sleep laboratory (N=1,741). The cohort

represents a random sample of men and women from the typical population in the Central Pennsylvania area, ranging in age from 20 to 100 years. As of October 31, 2003 120 deaths had been documented in this sample. Because men were evaluated first, their average followup time was approximately eleven years and approximately seven years for women. Sleep disordered breathing (SDB) was defined at four levels. These levels included: sleep apnea (OHI≥15), mild sleep apnea (snore + 15 >OHI>0), simple snore (OHI=0), and no SDB. Subjects were further grouped in terms of age (>55 years and ≤55 years), obesity (BMI>32 and BMI ≤32) as well as gender. The analysis was based on an accelerated failure time model weighted by sampling probability and assuming a Weibull distribution for the survival time. A relative survival time compared to the no SDB group was calculated.

Results: Within this sample the relative survival time across the three levels of severity of SDB compared to the no SDB group reflected a dose response pattern. The relative survival time also appeared to be associated with age, gender and obesity. The younger subjects with SDB had a shorter relative survival time compared to the older subjects with SDB (43.2% vs 86.3%). Women with SDB tended to have a shorter relative survival time than men with SDB (27.5% vs 66.5%). Obese subjects with SDB (BMI≥32) also tended to have a shorter survival time than nonobese subjects with SDB (41.2% vs 57.9%).

Conclusion: This is the first study to report mortality risk associated with SDB in a population sample. Specifically, subjects with sleep apnea (OHI≥15) compared to no SDB subjects were at increased risk for mortality. This risk was stronger in the young, in women and in the obese. The findings of this study do appear to confirm previous studies that were based on clinical samples. 1. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Chest 1988;98:9-14. 2. Ancoli-Israel S, Klauber MR, Kripke DF, Parker L, Cobarrubias M. Chest 1989;96:1054-1058. 3. Lavie P, Herer P, Peled R, et al. Sleep 1995;18:149-157. 4. Young T, Finn L. Thorax 1998;53:S16-S19. 5. Marti S, Sampol G, Munoz X, et al. Eur Resp J 2002;20:1511-1518.

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Prevalence And Clinical Significance Of Sleep-Related Breathing Disorder In End Stage Renal Disease

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Introduction: Several studies have shown that Sleep-related breathing disorder (SRBD) is quite common in end-stage renal disease (ESRD), and the prevalence has been estimated between 30% and 80%. The effects of SRBD on morbidity and mortality in ESRD patients are not well understood. Here, we present clinical impacts of SRDB in ESRD patients from the viewpoint of subjective daytime sleepiness, complication and prognosis.

Methods: One hundred and sixty seven subjects were studied (male: 95, female: 72, age: 30.1- 89.2: average age 63.7±10.5 year's old) out of 220 patients who underwent hemodialysis at Dialysis Center of Toyohashi Mates Clinic in Japan from 2001 to 2003. Written informed consent was obtained. SRBD variables were measured from standard polysomnogram (PSG) and subjective daytime sleepiness was evaluated from Epworth sleepiness scale (ESS). Background factors and vascular morbidities were also analyzed. Moreover, mortality follow up study of the subject patients was made during the two years period from the PSG examination.

Results: Average apnea-hypopnea index (AHI/hour) of all the subjects was 26.5±23.7. Ninety-four (56.3%) of ESRD patients had SRBD with AHI of 15 or more , and 58 (34.7%) patients showed severe SRBD with AHI of 30 or more. Only 8 (8.5%) patients with SRBD were aware of their own moderate to severe sleepiness (ESS score of more than 11 points), and we could not detect any difference in ESS score between the patients with and without SRBD. Prevalence of ischemic heart diseases and/or cerebrovascular strokes in the ESRD patient was 54.3% (51 patients), and incidence of these two disorders was significantly increased in proportion to SRBD severity (p=0.0001). Significant confounding factors for 15 or more of AHI in ESRD patients were sex (female, odds ratio-OR: 0.153,95%CI :0.053-0.443 , p=0.0005), age (OR: 1.061, 95%CI:1.017-1.108, p=0.0061), body mass index (OR: 1.171, 95%CI:1.026-1.336, p=0.0194) and histories of ischemic heart diseases or cerebrovascular strokes (OR: 3.289, 95%CI:1.473-7.340, p=0.0037). However, KT/V (dialysis adequacy) and change of body weight from pre-dialysis to post-dialysis did not appear to be significant confounding factors. Prevalence of ischemic heart diseases and/or cerebrovascular strokes in the subject patients were significantly increased by presence of diabetes mellitus (OR: 2.687, 95%CI:1.264-5.711, p=0.0102), SRBD (AHI≥15, OR: 2.525, 95%CI:1.163-5.483, p=0.0192), or history of treatment for hyper-parathyroidism (OR: 0.270, 95%CI:0.086-0.853, p=0.0257). Mortality analysis on elderly (60 years or older) 97 ESRD subjects without CPAP therapy indicated that survival rate of SRBD patients with AHI of 15 or more was significantly lower than that of the patients with AHI less than 15 during the follow up period (p=0.0406).

Conclusion: Our results confirmed that SRBD is remarkably high in ESRD patients. Although we could not identify the causative factor for the high prevalence of the disorder, SRBD in ESRD patients was strongly suspected to contribute to the occurrence of ischemic heart disease and /or cerebrovascular strokes. Moreover, SRBD in ESRD patients may act as an aggravating factor for the mortality during their clinical course.

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Intermittent Hypoxia Induces Erectile Dysfunction in Adult Male Rats

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Introduction: There is a strong clinical association between obstructive sleep apnea (OSA) and erectile dysfunction. Up to 45% of OSA patients have difficulty initiating or maintaining erections. Moreover, between 32-46% of all impotent patients are reported to have OSA. Finally, erectile function normalizes in approximately one third of OSA patients with erectile dysfunction when compliant on nasal CPAP. Intermittent hypoxia (IH), characteristic of OSA, is now regarded as a major cause of long-term physiological consequences, including sympathetic activation and autonomic dysfunction. Given the powerful anti-erectile role of the sympathetic nervous system and the role of autonomic dysfunction in impotence, we hypothesized that IH may be a major contributing factor in the development of erectile failure in OSA. To test this hypothesis, we recorded penile erections in freely moving rats before and after exposure to chronic IH.

Methods: Seven male Sprague Dawley rats were implanted with a telemetric transducer for a chronic recording of erectile tissue pressure. This technique has been validated for chronic penile erection recording in freely moving rats. Four days of continuous 24-hour baseline recordings of erectile activity were performed. All animals were then placed into

chambers in which O2 concentrations were cycled between 21% and 10% every 90 seconds during 12 hours of daylight (sleep period). For the remaining 12 hours of the night period, rats breathed room air. 24-hour recordings of erectile activity were made on a weekly basis for up to 8 weeks in the IH protocol.
Results: During baseline recordings, rats demonstrated 63.1±3.3 erections/day. The number of erections per day decreased to 51.5±2.5 erections ($p<0.05$) following the first two weeks of IH, followed by a persistent and progressive decline in erectile activity from weeks 3 to 8. By week 6 of chronic IH, erectile activity was decreased to 35.0±2.8 erections per day ($p<0.001$), and decreased even further by week 8 to 28.7±4.7 erections per day ($p<0.001$).
Conclusion: Rats exposed to chronic IH have a rapid and progressive decline in erectile function. Several hypotheses have been proposed regarding potential causes of erectile dysfunction in OSA, including decreased sexual desire from excessive daytime sleepiness and adverse physiological consequences of OSA. However, few studies have examined this clinical association. Moreover, clinical studies examining erectile dysfunction in OSA have been hampered by the common occurrence of comorbidities in OSA patients, such as hypertension, obesity, age and concomitant medication use. Finally, an animal model to examine the effects of OSA on erectile capability has been lacking. This study demonstrates for the first time that IH may be a major cause of erectile dysfunction, and suggests that patients with OSA who have frequent prominent oxygen desaturations may be at particular risk for developing impotence.

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Excessive Daytime Sleepiness: It Is Associated With More Than Apnea

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Introduction: Excessive daytime sleepiness (EDS) is commonly considered a cardinal sign of sleep apnea, which may lead to the neglect of other possible causal explanations. Limiting alternative factors for EDS could be one of the reasons for CPAP failure, especially in milder cases of sleep apnea. The purpose of this reanalysis was to assess the association between the complaint of EDS and sleep apnea considering a wide range of possible factors in a population sample.
Methods: We examined this question in the Penn State Cohort, which represents a random sample of 1,741 men and women from Central Pennsylvania, ranging in age from 20 to 100 years. The presence of EDS was established in terms of a moderate to severe complaint of EDS during the initial interview. The definition of SDB used in this study was obstructive apnea + hypopnea index ≥ 15. Additional variables evaluated in the Logistic Regression model included gender, age, BMI, diabetes, hypertension, allergy, asthma, depression, sleep disturbance (% 1, % REM & % sleep time), race, and alcohol or tobacco use.
Results: The standardized effect size based on the final Logistic Regression model indicated depression accounted for the largest proportion of the variance (see Table). This was followed by BMI, diabetes, age, smoking and finally sleep apnea. It is important to note that measures of sleep disturbance, gender, allergy, asthma, hypertension, alcohol use or race were not independently associated with EDS. Careful evaluation of the interaction between BMI and diabetes in this model indicated that BMI was independently associated with EDS only in the absence of diabetes, suggesting that diabetes was the more important factor. The strength of the association with EDS decreased with increasing age. Finally, the inclusion of milder forms of sleep disordered breathing including simple snoring reduced the strength of the association between EDS and BMI or diabetes suggesting that BMI and diabetes in the presence of milder forms of SDB compared to more severe forms of SDB are stronger risk factors for EDS. Table. Standardized effect size ES Depression 8.54 Log(BMI) 5.02 Diabetes 3.56 Age 3.20 Smoking 2.96 OHI≥15 1.89.
Conclusion: This analysis indicates that sleep apnea should not be considered the only possible cause for EDS. Further, when sleep apnea is associated with EDS it appears that the presence of EDS is more strongly associated with metabolic factors and/or obesity than with sleep disruption per se.1 In addition, the association with EDS was strongest in the young which is consistent with the findings that the most severe sleep apnea,2 the strongest association between sleep apnea and hypertension,3,4 and the higher mortality risk associated with sleep apnea are all in the young.5 1. Vgontzas AN, et al. J Int Med 2003;254:32-44. 2. Bixler EO, et al. Am J Respir Crit Care Med 1998;157:144-148. 3. Bixler EO, et al. Arch Int Med 2000;160:2289-2295. 4. Nieto FJ, et al. JAMA 2000;283:1829-1836. 5. Lavie P, et al. Sleep 1995;18:149-157.

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Lack of Hierarchy in Immediate Consequences of Respiratory Events in Sleep Disordered Breathing (SDB)

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Introduction: While there is evolving consensus on the operational definition of severe reduction in airflow (apnea), there remains considerable debate over events where reduction in airflow is more subtle (hypopneas and RERAs). Until recently the detection of immediate consequences (e.g. desaturation or arousal) of a respiratory event was essential to censor artifacts created by the respiratory recording technique. With the development of newer monitors for airflow, this may no longer be as critical. Furthermore, it has been assumed that there is an increasingly sensitive hierarchy of consequences for respiratory events (eg arousal is more "sensitive" than desaturation), and a definition of hypopnea based on events "validated" by arousal identifies all events "validated" by desaturation plus additional ones. The purpose of the present study was to determine the frequency and hierarchy of occurrence of O2 desaturation, EEG arousal and HR changes as immediate consequences of respiratory events in OSAHS to help identify any limitations of using a single one of these for validation of events.
Methods: 39 patients with suspected OSAS and 12 normal volunteers underwent full in-lab NPSG, including a nasal cannula for the detection of airflow. For each subject, 10 obstructive apneas (when available), 10 hypopneas and 20 non-apnea/non-hypopnea (NANH) events were randomly selected in each of NREM and REM sleep, for a target of 80 events per subject. Each event was reviewed for the presence of: 4% Oxygen desaturation within 30 seconds of event termination; EEG arousal (AASM criteria) within 5 seconds of event termination; and increase in heart rate (HR) of 6 bpm in the 10 seconds following the event. A cross tabulation of event type and consequences was then performed.
Results: In patients, 78% of obstructive apneas resulted in desaturation, 63% in EEG arousal and 73% in a HR increase. In hypopneas, consequences were also frequent: 54% had desaturation, 47% had EEG arousal and 55% had increase in HR. In the mildest (based on amplitude

reduction) events, 25% of events had desaturation, 42% had EEG arousal, and 42% had a HR increase. No differences were seen between events during NREM and REM sleep. The frequency with which the possible combinations of desaturation, EEG arousal and HR increase occurred showed no evident hierarchy. 20% of all events showed no consequence, 30% showed only 1 consequence, 30% showed 2 and 20% showed all 3 simultaneously. Of those with only a single consequence, one third of events showed desaturation only (10% of all events), one third showed EEG arousal only and one third showed HR increase only. Normal subjects showed fewer events (including no apneas) but a similar lack of hierarchy of consequences. In both patients and normal subjects, O2 desaturation did not uniformly imply EEG arousal or an increase in HR, and EEG arousal did not uniformly predict an increase in HR.
Conclusion: Our data show that in OSAHS consequences of individual respiratory events, ie O2 desaturation, EEG arousal and HR changes, overlap but do not occur in a consistent hierarchical manner. Most importantly, no one consequence occurred after every event that had any consequence. Thus, if one wishes to validate the flow based definition of events using consequences, no single consequence validates all reductions of airflow as hypopnea without missing some events that would have been validated by the other consequences. Our data leads us to believe that, with the development of newer monitors for airflow, the role of "consequence" could shift from their present role in elimination of artifact to representing an independent characteristic of the event with potential physiological significance. The relationship between physiological consequences of respiratory events and symptoms/outcomes of OSAHS should be most effectively evaluated if one captures all changes in breathing and tabulates their consequences without losing potentially relevant events due to a priori assumptions.

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Rapid Eye Movement-Related Obstructive Sleep Apnea (REM-OSA): A Subset of Obstructive Sleep Apnea (OSA) or a Distinct Entity?

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Introduction: Little data are available regarding the prevalence and characteristics of REM-OSA. We describe the prevalence and characteristics of REM-OSA.
Methods: We conducted a retrospective review of polysomnography reports of patients diagnosed with OSA at The Cleveland Clinic Foundation between July 1st, 2000 and October 30th, 2003. REM-OSA was defined as: overall apnea-hypopnea index (AHI)≥ 5, REM-AHI>5, non-REM-AHI (NREM-AHI)<5. We determined the prevalence and characteristics of REM-OSA. Correlation of REM-OSA with age, gender, body-mass index (BMI), Beck depression inventory (BDI), and Epworth sleepiness scale (ESS) was performed.
Results: 3088 patients were diagnosed with OSA between July 1st, 2000 and October 30th, 2003. 287 patients satisfied our criteria for REM-OSA diagnosis (9.3%). The mean plus or minus standard deviation for the different characteristics were: age (45.22±13.50) years, BMI (33.31±8.60) Kg/m2, ESS (11.47±5.47), BDI (10.37±7.94), AHI (7.36±2.42), REM-AHI (29.75±15.48), NREM-AHI (3.07±1.32). The percentage of women in the REM-OSA group was 55.1% versus 27.8% in the OSA group (p value <0.001). A very weak correlation was found between REM-AHI and BMI (r=0.27), but none was detected between REM-AHI and any of the other characteristics.
Conclusion: REM-OSA represents a significant proportion of patients with OSA and appears to have a different gender predilection. It may represent a distinct subgroup with characteristics different from the ones established for OSA

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Blood Pressure And Apnea Induced Skin Circulatory Response After Antihypertensive Treatment In OSA Patients

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Introduction: Obstructive sleep apnea (OSA) has been found to be the most common cause of secondary hypertension. Although continuous positive airway pressure treatment could reduce the blood pressure (BP), the elimination of apnea could not normalize BP in all the hypertensive OSA patients. The present study was aimed to compare the effect of Doxazosin (a peripheral α-receptor inhibitor) and Enalapril (an ACE inhibitor) on BP and apnea induced digital skin vasoconstriction in hypertensive OSA patients.
Methods: A double-blind cross-over study on Doxazosin (8mg o.d.) and Enalapril (20mg o.d.) was undertaken in 14 male hypertensive OSA patients (age 55.0±1.7 yrs, BMI 30.1±1.0kg/m2, AHI 42.2±21.3 event/hr). Following a three-week washout period, patients received two weeks treatment with lower dosage (Doxazosin 4mg o.d. Enalapril 10mg o.d., respectively) and titurated to the target dosage for an additional two weeks. 24-hour ambulatory BP, full-night polysomnography with peripheral arterial tonometry (PAT) and continuous non-invasive BP monitoring (Finarpres) were performed at the end of each treatment period. Skin circulatory changes during and following apnic event were expressed as a ratio (PAT ratio) between the 3 nadir pulse amplitudes during 21 seconds following apnea and the 3 peak pulse amplitudes during apnea.
Results: Compare to Doxazosin, office systolic BP (p=0.047) but not diastolic BP was significantly lower after Enalpril treatment while 24-hour BP (or day/night portions) did not differ. The PAT ratio after Doxazosin was 40.1±9.8% and after Enalapril was 32.0±11.2% (p=0.006). Differences encompassed both REM and nREM sleep. There was no difference in OSA severity between the two treatments.
Conclusion: Skin vascular responses following apnea are at least in part α-receptor mediated. The antihypertensive effect of Doxazosin was proportionally weak in hypertensive OSA patients and the mechanism behind this phenomenon needs to be further analysed.

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Prevalence Of Obstructive Sleep Apnea In Patients Surviving Ischemic Stroke

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Introduction: Sleep disordered breathing (SDB) has been observed to be a pre-event characteristic of many patients who experience stroke (CVA). Also, surviving a CVA has been reported to increase the likelihood of SDB. SDB has been associated with comorbidities in the general population and may potentially have a negative impact on the recovery trajectory of CVA survivors. Therefore, a cost-effective and accessible tool for identifying SDB would have clinical value. To assess the prevalence and severity of SDB in patients who had recently survived the acute CVA trauma phase and were deemed stable, we employed a portable system to quantify apneas (obstructive (OA), central (CA),

mixed (MA)) and blood oxygen saturation (SpO2).
Methods: Recent survivors of ischemic CVA participated in the study (N = 18; n = 12 females; age = 63 ± 14 years; n = 14 right hemisphere lesions). Patients were evaluated for SDB within 72 hours of the stroke diagnosis or when they were considered to be stable. CVA foci were determined and severity was quantified with the Functional Independence Measure (FIM). All relevant respiratory variables and finger tip pulse oximetry were recorded with a previously validated portable monitoring system (LifeShirt®, VivoMetrics, Inc.; Ventura, CA). Presence of SDB was defined as an apnea hypopnea index (AHI) > 10. SDB events associated with a drop in SpO2 of 3% or greater were classified as desaturation events. Sleep time was estimated from technician recorded Lights-off to Lights-on for the calculation of AHI ([apneas + hypopneas]/sleep time) and oxygen desaturation index (ODI; desaturation events/hour).
Results: Fifteen patients (87%) exhibited an AHI > 10. For this subgroup, FIM score at the time of admission was (mean ± SD) 65 ± 15. AHI was 34 ± 14 events per hour. Total SDB events were: OA = 148 ± 11; MA = 57 ± 67 and CA = 5 ± 14. Blood oxygen desaturations were common (mean nadir SpO2 = 79 ± 0.1%), as was the frequency of desaturations events (ODI = 45 ± 15).
Conclusion: Theses data enrich previous observations of the prevalence of SDB in patients who have recently survived stroke, as well as suggest that SDB can be efficiently identified by this portable system in this population.

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Positive Airway Pressure Gas Modulation In The Treatment Of Complex Sleep Disordered Breathing
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Introduction: Abnormal CO2 homeostasis (hypocapnia) drives complex forms of sleep-disordered breathing, especially idiopathic central sleep apnea, periodic breathing at altitude and sea level, and Cheyne-Stokes respiration in congestive heart failure. Increasing CO2 in a variety of ways (inhalation, dead space) has been used to treat obstructive and non-obstructive sleep-disordered breathing. This report describes the use of CO2 with positive airway pressure (PAP) using a prototype device, the Positive Airway pressure Gas Modulator (PAPGAM), to treat severe mixed sleep-disordered breathing.
Methods: Six male patients (age 54± 5.7 years) with severe poorly controlled mixed sleep-disordered breathing in the absence of renal or heart failure were studied with Institutional IRB approval. Routine full polysomnography montage was enhanced by end-tidal (special sealed oronasal mask) and transcutaneous CO2 measurements. The PAPGAM was designed to deliver precisely metered dosages of medical grade CO2 in conjunction with conventional PAP. It contains a computer-controlled proportional valve that modulates the delivery of CO2 gas into a chamber where it is mixed with pressurized room air from a PAP machine. There are multiple redundant loops of safety controls. Air in the mixing chamber and at the mask is continuously sampled for CO2 concentration. Once the subject was sleep, and sleep-disordered breathing evident, CO2 was added to the circuit at 0.25% increments.
Results: Pre-treatment RDI was 66± 14.5 / hour of sleep, with a nocturnal desaturation low of 84.6±10.1 %. Residual RDI on best treatment was 43.1± 9 / hour of sleep. Five of six patients demonstrated mild relative sleep-hypocapnia. No patient required to have an increase in sleep end-tidal or transcutaneous CO2 of more than 3-4 mm Hg. There was no discomfort, shortness of breath, palpitations, headache, or significant increase in respiratory or heart rate. The dose range of response was 0.5 to 1.5%. Two subjects required 0.5%, two required 0.75%, one each for 1%, and 1.5%. The residual RDI on CO2, scored irrespective of desaturations, was in the normal range (≤ 5 / hour of sleep). There was an immediate (< 1 minute) response to addition of CO2, and minimal changes were required to be made across a night. Two subjects had a second night at the dose of CO2 determined to be efficacious, with no required dose change. No adverse effects on overall sleep architecture were noted.
Conclusion: We demonstrate the single-night efficacy of low doses of CO2, used as an adjunct to routine PAP therapy utilizing a prototype device. The effective dose was unexpectedly small (0.5 to 1%). Important differences from prior work includes: 1) Use of a closed loop system that maintains a specific CO2 concentration regardless of flow rate; 2) Scoring the entire spectrum of respiratory events regardless of desaturation, which accurately reflects the whole burden of sleep-disordered breathing; 3) A population of mixed disease rather than central sleep apnea / Cheyne-Stokes respiration, suggesting broad applicability; 4) Expanding the concept of therapeutic gas modulation; 5) The apparent synergism between positive airway pressure and CO2.

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In-Office Screening for Obstructive Sleep Apnea in Primary Care
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Introduction: While obstructive sleep apnea (OSA) is common among middle-aged adults (NEJM 1993;328:1230), its occurrence among individuals with hypertension is still greater (NEJM 2000;342:1378). OSA may be particularly important in individuals with hypertension that is refractory to traditional treatment approaches (Sleep 2001;24:721). We did a prospective comparison of four methods that could signal the presence of sleep apnea among patients with diagnosed hypertension. All were methods that could be performed effectively at the bedside by the primary care provider. These included a composite score that assessed frequency of apnea-related symptoms; body mass index (BMI); oral cavity measurements, and symptom score taken together with BMI. We scored responses to three questions related to apnea symptom-frequency on a Likert scale, and averaged the responses to obtain our composite symptom score. We chose BMI as a second strategy because it is a surrogate for obesity, which is strongly associated with apnea. We also chose the multivariable apnea prediction (MAP) questionnaire (Sleep 1995;18:158), which assesses relative risk for apnea, by combining the composite symptom frequency score described above with other apnea-related variables — BMI, age, and gender. Historically, the advantage of this MAP score has been its usefulness in settings where BMI is low. We chose oral measurements, because this was a previously validated measure among general populations (Ann Int Med 1997;127:581) outside of sleep referral settings. However, application of this method requires that subjects have adequate dentition.
Methods: We recruited subjects from primary-care outpatient settings at the Philadelphia Veterans Affairs Medical Center and from the University of Pennsylvania Hypertension outpatient practices. Subjects' ages ranged from 30-65 years. All had hypertension diagnosed by a health care provider, or were taking antihypertensive medications. Anyone with known OSA, or any condition associated with nocturnal hypoxia, or those using supplemental oxygen were excluded. We used the apnea-hypopnea index on 12-channel, in-laboratory polysomnogra-

phy as the criterion standard, and compared it against each of the predictors - symptom score, BMI, oral cavity measurements, and symptoms together with BMI (MAP). We assessed apnea as present when the apnea-hypopnea index was >= 15 events/hour. We did area-under-curve analysis for receiver operating characteristic curves using the c-statistic on a logistic regression using SAS.
Results: We enrolled 230 subjects, and received usable symptom data on 213 (93%), BMI data on 229 (99.6%), oral measurements on 161 (70%), and calculated MAP scores on 225 (98%). Our analysis revealed AUC values as follows: 0.626 for symptoms alone, 0.658 for BMI, 0.684 for oral measurements, and 0.734 for symptoms together with BMI.
Conclusion: Data regarding symptoms, and data to compute BMI and the multivariable prediction index could be obtained on the majority of subjects. On the other hand, the oral measurement approach was less useful because it could not be obtained in the largest number of subjects. Symptoms taken alone were least useful for predicting the presence of sleep apnea. BMI was a stronger predictor, and oral measurements performed slightly better. Symptoms combined with BMI had the strongest discriminatory power in our study, and may represent a potential means of risk-stratification of subjects presenting to an ambulatory practice setting with OSA.

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Sleepiness: Convergence Of The Alpha Attenuation Test (AAT) And Spectral EEG Measures

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Introduction: The alpha attenuation coefficient (AAC), the ratio of alpha power with eyes closed to eyes open during a standard alpha attenuation task (AAT), has been purported to be a valid objective measure of sleepiness. We evaluated both the concurrent and predictive value of the AAC before and after the experimental induction of stress in a group of patients with suspected Obstructive Sleep Apnea. Specifically, we believed that sleepier subjects would be less affected by the stressor than would more alert subjects, as assessed by the AAC.
Methods: Subjects were 15 males and two females, ages 28 to 65, being evaluated for Obstructive Sleep Apnea. Subjects were told that the purpose of the study was to assess patients impressions of the sleep lab environment. Electrode application was followed by the standard AAT (30 seconds eyes open, 30 seconds eyes closed, repeat). After this baseline AAT we added a stressor to induce arousal in half the subjects. Anxiety was induced by informing subjects they would need to prepare a ten-minute talk about their experience in the sleep lab that would be discussed before a panel of doctors later that evening. The non-stress group was told that they would fill out a questionnaire about their sleep lab experience. A second AAT was conducted 15-20 minutes later.
Results: A significant correlation was shown between AAC (smaller values indicate greater sleepiness) during the baseline AAT and the Epworth Sleepiness Scale (N = 17, r = -.61, p=.05). Correlations for AAC and theta power (r = -.38), delta power (r=-.38), and beta power (r = .35) were in the expected direction but not statistically significant. Two groups (high and low sleep need) were formed from the talk group based on a median split. Spectral EEG analysis of the data collected from the baseline AAT to the second AAT (post stress induction) showed that both groups were statistically unaffected by the stress induction across all spectral bands. However, across both times the high sleep need group exhibited higher delta power (F(1,7)=21.9, p=.002) and marginally higher theta power across both conditions (F(1,7)=3.0, p=.13).
Conclusion: Contrary to one of our central hypotheses, obstructive sleep apnea patients were not appreciably aroused after anxiety induction regardless of level of sleep need. Spectral power across all bands remained relatively stable between baseline AAT and the post-stress AAT. However, of equal interest in this study was the further confirmation that AAC not only correlates with sleepiness as assessed by the Epworth Sleepiness Scale, but that it is related to identifiable physiological correlates, in this case heightened delta and theta power. These findings further validate the AAC as a measure of sleepiness.

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Self-Efficacy and Adherence to CPAP Therapy

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Introduction: Although nasal CPAP is the primary treatment for OSA, adherence remains problematic with only half of all patients using the treatment on a routine basis. Studies show long-term adherence to CPAP is established within the first week of treatment. Although a large number of factors have been proposed to affect CPAP adherence, none have been shown to reliably predict which patients will be non-adherent to CPAP therapy. The purpose of this study was to determine which pretreatment variables are associated with CPAP adherence during the first week of treatment.
Methods: A convenience sample of 55 clinic patients suspected of having OSA was recruited. Inclusion criteria were: age 20-60; AHI ≥ 5; and a candidate for CPAP. Variables measured were gender, age, AHI, BMI, claustrophobia, (Fear and Avoidance Scale), perceived OSA and CPAP self-efficacy (Self-Efficacy Measurement for Sleep Apnea [SEMSA], subjective sleepiness (Epworth Sleepiness Scale [ESS]), sustained vigilance (Psychomotor Vigilance Task [PVT], mood (Profile of Mood States [POMS], cognitive processing (Digit Symbol Substitution Test [DSST], activation (Activation-Deactivation Adjective Check List [AD-ACL), health status (SF-36), and functional status (Functional Outcomes of Sleep Questionnaire [FOSQ],). All measures were administered pretreatment and the SEMSA was administered a second time after at least 7 days of CPAP. Using the AutoSet clinical system set to constant pressure mode, adherence was measured by the mean nightly duration of effective CPAP pressure.
Results: The sample (58% male, 53% African-American, age = 46.6 yrs ± 9.6, mean BMI 39.02 kg/m2 ± 9.4, AHI = 44.17 ± 30.7) was subjectively sleepy (mean ESS = 14.1 ± 5.8) and had impaired sustained vigilance (mean PVT lapses per trial = 6.79 ± 9.48). Mean effective duration of CPAP was 4.9 hrs ± 2.09. There were no significant associations between CPAP adherence and gender, age, AHI, BMI, ESS, FAAS, SF-36, PVT, FOSQ, DSST, and pre-treatment SEMSA. However, there were significant associations between CPAP adherence and POMS vigor (r = -0.34, p = 0.02) and fatigue (r = 0.41, p = 0.006) subscale scores and total mood disturbance score (r = 0.32, p = 0.04), general activation subscale on the AD-ACL (r = 0.38, p = 0.01), and post-treatment perceived self-efficacy (confidence to use CPAP) score on the SEMSA (r = 0.31, p = 0.04).
Conclusion: Consistent with previous findings, CPAP adherence does not appear to be related to disease severity or pretreatment sleepiness. On the other hand, it does have a modest relationship with a sense of pretreatment vigor and fatigue. Not surprisingly, patients who were more adherent to CPAP during the first week of treatment also tended to report greater confidence in using CPAP.

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Effect of Expiratory Pressure Relief During Continuous Positive Airway Pressure Therapy on Adherence in a Retrospective Analysis of Recent Clinical Experience

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Introduction: Many factors may influence compliance and adherence to continuous positive airway pressure therapy. Pressure relief during exhalation may offer additional comfort and provide a compliance advantage. The recent introduction of C-Flex® offers such relief. A retrospective analysis of device download data in a clinical setting may offer insight into the effect of this enhanced therapy.
Methods: A retrospective analysis of therapy compliance data was performed with Institutional Review Board approval. Subjects were selected from a sequential series of clinical sleep laboratory patients. Patients were diagnosed and titrated in the sleep laboratory using full polysomnography, employing AASM standard methodology. Both conventional CPAP (CPAP) and CPAP with flexible pressure relief (FLEX) were used in recent clinical practice. Both modes of therapy were implemented on the same CPAP device (REMStar Pro, Respironics, Inc., Murrysville, PA, USA). Heated humidification was available to all patients and was used by most. All patients received standardized training on equipment and mask fitting. Patients routinely provided compliance data as part of a structured follow program at the Sleep Disorders Center. Data were stored on a SmartCard, and downloaded into Encore Pro Compliance software for archiving, reporting and analysis. Average number of hours of use and number of days of use were recorded for each patient. Patients were said to have a compliant night if they slept more than 4 hours during the night. Percentage of Compliant nights is reported for each subject. Summary data were generated by the compliance software, with subsequent appropriate statistical analysis performed. Descriptive statistics are reported. Two-tailed comparison between therapies were performed using either t-test (if normal distribution) or Wilcoxon Signed Rank. Data are reported mean ± standard deviation.
Results: A total of 96 subjects (75 FLEX, 21 CPAP) were included in the analysis. CPAP patients were on therapy a longer period than FLEX patients (293 ± 291 days CPAP vs. 49 ± 42 days C-Flex, $p<0.001$). Average hours of use per night was significantly longer for patients on FLEX v. CPAP therapy (5.06 ± 1.80 hours v. 3.96 ± 2.63 hours respectively, $p=0.029$). FLEX demonstrated a significantly higher number of compliant nights (68.0 ± 28.0 % v. 51.6 ± 34 %, respectively, $p=0.025$).
Conclusion: Review of recent clinical therapy experience suggests a compliance advantage for the C-Flex v. CPAP mode in a general clinical sleep medicine practice.

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Obstructive Sleep Disordered Breathing in Major Depressive Disorder

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Introduction: Depressive symptoms are common in patients with obstructive sleep-disordered breathing (OSDB). Auditory sleep fragmentation can induce depressed mood, and functional imaging in patients with OSDB has shown reduced prefrontal function, similar to MDD. The prevalence of OSDB in populations with a primary diagnosis of major depressive disorder (MDD) is not clear. Standards of measuring and scoring respiratory events have changed, and the use of nasal-pressure based sleep-breathing diagnostics can more accurately define a pathophysiological relationship. The present study aimed to examine the relationship of the whole spectrum of abnormal respiratory events with clinical symptoms of MDD.
Methods: The overnight sleep-breathing of twenty individuals with MDD, unselected for sleep related complaints, and fifteen non-depressed controls subjects were recorded using an unattended nasal pressure-based home sleep monitoring device, Stardust SystemTM. The device recorded nasal airflow, breathing effort, heart rate, oxygen saturation, and body position. Major and minor obstructive respiratory events were scored based on the morphology of the nasal pressure trace. Oxygen desaturation indices were calculated. Correlations of respiratory variables with MDD symptoms were computed. Standard questionnaires evaluated sleep quality, subjective daytime sleepiness and circadian preference.
Results: Pittsburgh sleep quality but not Epworth sleepiness or Horne-Ostberg scores were significantly different in the depressed versus the controls. Analysis of variance revealed that the two groups varied significantly on four variables: major flow-limitation events, major flow-limitation accompanied by a desaturation, minor flow-limitation accompanied by a desaturation, and average nocturnal saturation. Sleep breathing variables (minor events, minor events accompanied by a desaturation, major events, major events accompanied by a desaturation, number of desaturations per hour, average desaturation throughout the evening) correctly discriminated 81.3% of those with major depressive disorder and 71.4% of the non-depressed participants.
Conclusion: These results suggest that OSDB, by causing chronic sleep fragmentation, may be more important than previously recognized in the etiology, course and treatment of MDD. Accurate sleep-breathing assessments may usefully contribute to the management of MDD patients.

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The Gender of Obstructive Sleep Apnea Patients does not determine their Adherence to CPAP Therapy

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Introduction: Obstructive sleep apnea (OSA) is a widely prevalent disorder associated with increased healthcare utilization, decreased productivity and an increased risk of accidents. Long-term treatment of OSA with CPAP improves cognitive and somatic parameters. While factors such as education and intensive follow-up have been suggested to determine adherence to CPAP therapy, gender-related differences in adherence to CPAP therapy have not been evaluated systematically. It is conceivable that behavioral, psychological, social and symptomatic differences between male and female patients may lead to gender-related differences in adherence to CPAP therapy.
Methods: Patients with newly diagnosed OSA started on CPAP therapy at Sleep Disorders Center at Henry Ford Hospital are randomly given a SMART-Track modem (DeVilbiss, Colorado), which is connected to the CPAP device and retrieves, analyzes, and stores the patient CPAP usage data for the first 31 days (eCompliance). The charts of all women diagnosed with OSA over past six months with eCompliance analysis (n=21) and an equal number of male patients with OSA on eCompliance, select-

ed over the same time period, were reviewed.
Results: Male and female cohorts were similar in terms of age (54 years vs. 52 years), racial distribution (55% Caucasian and 45% African-American vs. 60% Caucasian and 40% African-American), neck size (18 inch vs. 16 inch), Epworth sleepiness score (ESS, 12 vs. 14), self reported hours of sleep (7.1 hours vs. 6.6 hours), sleep latency (12.7 minutes vs. 10.7 minutes), sleep efficiency (79.8% vs. 79.9%), average oxygen saturation (91% vs. 90.5%), lowest oxygen saturation (76% vs. 73%), apnea-hypopnea index (AHI) during non-REM sleep (44/hour vs. 48/hour) or total AHI (43/hour vs. 48/hour). BMI (41 vs. 37, P=0.09) and AHI during REM sleep (45/hour vs. 30/hour, P=0.06) were slightly, but not significantly, higher in females. There were no significant differences between the male and the female groups in average daily hours of CPAP use (5.0 hours vs. 5.3 hours), percentage of days there was any use of CPAP (82% vs. 84%) and the usage index, i.e., the percentage of days CPAP was used for 4 or more hours (59.3% vs. 59.9%). There was a trend towards usage to be higher in Caucasian (n=23) than African-American (n=17) population in terms of average daily use (5.6 hours vs. 4.4 hours, P=0.07), and usage index (64% vs. 50%, P=0.17). Average daily hours of CPAP use correlated negatively with sleep latency (r=-0.32, P=0.04), but not with age, BMI, neck size, ESS, average or lowest oxygen saturations or AHI. When the male and female groups were analyzed separately, a significant correlation was seen between the usage index and ESS (r=0.46, P=0.04) in women, but no other variables in either gender.
Conclusion: Our results fail to demonstrate significant gender-related differences in adherence to CPAP therapy for OSA. CPAP usage also did not correlate with daytime symptoms or demographic or polysomnographic variables other than sleep latency in all patients and ESS in women. Further studies are needed to explore factors determining adherence to CPAP to develop relevant health initiatives targeting particular areas to optimize the utilization of this therapy.

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Plasma Levels Of B-Type Natriuretic Peptide In Patients With Obstructive Sleep Apnea Syndrome

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Introduction: B-type natriuretic peptide (BNP) has been proven to be a biochemical marker of severity of congestive heart failure (CHF). Obstructive sleep apnea symdrome (OSAS) is known to cause CHF. The aim of the study is to evaluate BNP secretion in patients with OSAS.
Methods: Plasma BNP was measured at the early morning after polysomnography in 262 patients with mild to severe OSAS and 75 normal subjects. We excluded the patients with chronic lung disease, ischemic heart disease, diabetes mellitus or definite heart failue. Moreover, we investigate the interval changes of BNP after 3 months of effective nasal continuous positive airway pressure (CPAP) treatment in 23 patients with severe OSAS and effectine oral appliance (OA) treatment in 20 patients with moderate OSAS.
Results: The frequency of patients with elevated plasma BNP levels (>40pg/ml) in moderate and severe OSAS were higher than in mild OSAS and normal subjects. Both effective CPAP treatment and OA treatment significantly reduced plasma BNP levels.
Conclusion: Moderate to severe OSAS patients have abnormal BNF secretion. Effective nasal CPAP or OA therapy led to normalization of BNF secretion during sleep.

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Oxidative Stress Reactions In The Cat Brain Induced By Periods Of Recurrent Apnea

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Introduction: Oxidative stress has been linked to several neurodegenerative diseases; in this regard, an increase in free radicals has been reported in Alzheimer's disease (Sayre LM et al., J. Neurochem. 68:2092-2097,1997; Smith MA et al., Free Radic. Biol. Med. 32:1049, 2002). One of these is peroxynitrite (ONOO-), which is a toxic oxidizing agent produced by the reaction of NO with superoxide anions (O2.-). Peroxynitrite induce nitration of tyrosine residues; such alterations lead to changes in protein structure and function (Squadrito GL et al., Free Radic. Biol. Med. 25:392-403, 1998). Antibodies to nitrotyrosine have been used to monitor the status of peroxynitrite-induced modification of proteins (Squadrito GL et al., Free Radic. Biol. Med. 25:392-403, 1998). In our previous study, we have found neuronal degeneration in certain brain regions in an animal model of recurrent apnea; we hypothesize that such damage may, at least partially, be due to free radicals generated by the apneaic condition.
Methods: An experimental group of cats were treated with 3-6 hours of recurrent apnea; control cats underwent the same surgical procedures as the experimental animals but were not subjected to recurrent apnea. The hippocampus and cerebral cortex from both experimental and control cats were obtained following transcardial perfusion with a fixative containing paraformaldehyde and glutaraldehyde. Immunohistochemical techniques (ABC method) were used to stain frozen sections (25 _m-thick) with anti-nitrotyrosine antibody (Alpha Diagnostic Int., San Antonio, TX, USA; code NITT-12A). Labeled neurons were identified by the DAB color reaction and observed under light microscopy.
Results: In the hippocampus, neurons labeled by anti-nitrotyrosine antibody were observed mainly in the CA1 region; CA2, CA3 contained only a few positive cells. Most neurons labeled in CA1 were located in the strata pyramidal, only a few positive neurons were present in the strata radiatum and the strata oriens. The granule cell layer of the dentate gyrus contained very few positive cells; however, the hilus contained many labeled polymorphic neurons. In the cerebral cortex, very few faintly labeled neurons were observed in the prefrontal and cingulate cortices. However, a great many positive neurons were present in the insular cortex and the amygdala. No positive neurons were observed in any preceding regions of control cats.
Conclusion: Our results clearly demonstrate, that during recurrent apnea, neurons in the hippocampus and certain areas of the cerebral cortex (prefrontal, cingulate and insular) as well as the amygdala are subjected to oxidative stress. These results may provide a basis for understanding the functional deficits that occur in individuals that experience periods of recurrent apnea.

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Quantification of Alertness, Memory and Neurophysiological Changes in Sleep Apnea Patients Following Treatment with nCPAP

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Introduction: Sleep Apnea (SA) patients treated with nCPAP during a 3-month study were repeatedly evaluated with an alertness and memory profile (AMP) with simultaneous acquisition of neurophysiological data. Each AMP session included a 3-Choice Psychomotor Vigilance Test, Verbal/Image Paired Associate Learning/Memory tests and a Sternberg Memory-Scan.
Methods: Forty-three patients (28 males; 15 females; mean age=49.7, range 31-71) diagnosed with SA (mean RDI=43.7, range 9-112) were evaluated during up to five AMP sessions. Sample sizes at time-points following pre-treatment were variable, because the study is not yet complete. Scheduled evaluations were conducted at 2-weeks (n=28), 1-month (n=26), 2-months (n=13) and 3-months (n=7) post-treatment with nCPAP. SA patients were compared to 47 healthy subjects (males=23; females=24; mean age=41.1, range 25-70) evaluated at the same five time-points. Continuous EEG (bipolar FzPOz and CzPOz, 256 samples/second, bandpass 0.5 Hz and 65Hz) was acquired during the AMP using a wireless sensor headset and automated B-AlertTM software to quantify the level of alertness during the session. Vigilance accuracy (VigAcc), vigilance reaction times (RT), number of lapses, accuracy across all memory tests (MemAcc) and percentage of EEG classified as drowsy were computed for each subject. These variables were z-score transformed relative to the healthy subjects.
Results: SA patients evaluated pre-treatment evidenced significantly lower VigAcc ($t=2.97$, $p<0.005$) with more lapses ($t=-3.71$, $p<0.001$), slower RT ($t=-3.35$, $p<0.001$), decreased MemAcc ($t=5.18$, $p<0.001$) and increased EEG classified as drowsy ($t=-2.30$, $p<0.05$) when compared to the healthy group during session one. To assess the effects of nCPAP, patient data were z-scored to the healthy population. After 2-weeks of treatment, one-third of the SA patients evidenced improved performance, however, only MemAcc achieved significance ($t=-2.51$, $p<0.05$). After 1-month, VigAcc ($t=-2.17$, $p<0.05$) and MemAcc ($t=-2.79$, $p<0.01$) increased. After 2-months, significant decreases in RT ($t=3.18$, $p<0.01$) and percent EEG drowsy ($t=2.18$, $p<0.05$) were also observed. Although the sample size at 3-months was insufficient for statistical comparison, mean values suggested that patients continued to show improved memory and vigilance performance with decreased drowsy EEG. Using z-score thresholds that classified 95% of the healthy subjects as normal, the percentage of SA patients outside the normal range for VigAcc, lapses, and MemAcc decreased from 42-49% at baseline to 21-25% after one month of nCPAP.
Conclusion: Substantial data support the association between neurocognitive dysfunction and SA. Evidence-based outcome studies documenting improved cognition following nCPAP treatment are more limited. AMP provided rapid, repeatable quantification of the daytime symptoms of SA using neurophysiological and performance measures during vigilance, learning and memory tasks. Although a sub-group of SA patients evidenced improvements in alertness and memory after 2-weeks of treatment, some patients did not improve until after one- or two-months of treatment. Variability in the timecourse of nCPAP in ameliorating the neurocognitive deficits was most frequently associated with the time required for individual patients to adapt to nCPAP. Interestingly, patients continued to evidence improvements in alertness and memory at the 2-month and 3-month sessions, suggesting the potential value of more longitudinal studies with testing at 6- and 12-month intervals.

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Ethnicity, Self-Regulation, and CPAP Use in Obstructive Sleep Apnea (OSA)

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Introduction: Sleep-disordered breathing has been estimated to be about twice as prevalent in Hispanics and African-Americans as Caucasians. However, adherence to CPAP is considered to be low for all ethnic groups. This study investigates whether adherence to CPAP differs among ethnic groups, whether the barriers to CPAP use also vary with ethnicity, and whether a four-phase cognitive-behavioral model of self-regulation (OSA symptom avoidance, OSA acceptance, OSA compliance, and OSA self-regulation in a sequentially improving order) predicts any ethnic differences in adherence to CPAP.
Methods: Patients newly diagnosed with OSA in the Columbia University Sleep and Ventilatory Disorders Laboratory were prescribed their successfully titrated levels of CPAP using a machine which monitored time at the prescribed pressure (ResMed, Elite). Phase of OSA self-regulation, and barriers to CPAP use were assessed by analysis of responses to a qualitative research instrument, the OSA Self-Regulatory Development Interview (OSASRDI) at 30-day and 60-day follow-ups. Data were analyzed using ANOVA and non-parametric tests. A significance level of alpha = .05 was used for all statistical tests.
Results: Twenty seven patients presented for 30-day follow-up. Of these, 15% were African-American, 11% were Asian-American, 30% were Hispanic, and 41% were Caucasian. There were no significant differences among the groups in OSA severity at baseline. At 30-day follow-up, there were no significant group differences in CPAP use or phase of self-regulation. Nineteen of the 27 participants presented at 60-day follow-up. Significantly fewer African-Americans and Hispanics who presented at 30-day follow-up also presented at 60-day follow-up than did Caucasians and Asian-Americans (50% versus 92.9%, $p=.049$). Attendance at 60-day follow-up was not related to severity of OSA at baseline, age, gender, whether another adult lived with the patient, or proximity to the sleep laboratory. Self-regulation phase at 30-day follow-up did not predict 60-day presentation for minorities. However, significantly more Caucasian and Asian- Americans who were OSA compliant or OSA self-regulatory at 30-day follow-up presented at 60-day follow-up than did Caucasians who were OSA avoidant or OSA acceptant, or African-American and Hispanics who were OSA compliant or OSA self-regulatory at 30-day follow-up (100% versus 53.3%, $p=.008$). Individual responses to the OSASRDI at 30-day follow-up showed no consistent differences in barriers to CPAP use between African-American and Hispanic non-presenters at 60-days and 60-day presenters of all ethnicities.
Conclusion: African-American and Hispanic OSA patients were more likely to be lost to follow-up at 60-days than Caucasians and Asian-Americans in this structured protocol. We speculate, therefore, that African-Americans and Hispanics with OSA may be less likely to follow through with CPAP use in the longer term than Caucasian and Asian-Americans, although barriers to such follow up remain to be determined. Self-regulatory phase may not play a role in repeated follow-up attendance for African-Americans and Hispanics, but seems to contribute to such follow-up attendance for Asian-Americans and Caucasians.

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Central Apnea During Positive Therapy Titration Polysomnograms. Role Of Circulation Time In Predicting Associated LV Failure

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Introduction: Central sleep apnea (CSA) is becoming a commonly recognized, often challenging sleep disorder seen in sleep laboratories, particularly when this emerges during positive pressure therapy titration polysomnograms (PSG). Although the conditions that can cause CSA are heterogeneous, some major factors implicated for this phenomenon include: obstructive sleep apnea resembling CSA, positive pressure induced CSA, and emerging Cheyne-Stokes respiration (CSR) associated with underlying cardiac dysfunction. Measurement of circulation time and periodic breathing cycle length has been suggested to differentiate patients with CSA with and without heart failure. The specific aim of our study was to predict the etiology of central apnea by evaluating polysomnographic features including circulation time (CT), interapnea recovery breathing time (IARBT) and clinical findings.
Methods: ±We performed a retrospective review of our database for patients with CSA present in (PSG) tracings while they were titrated with CPAP or BiPAP as a treatment of their sleep related breathing disorder. Once a case was identified, several parameters were collected including demographics, Epworth sleepiness score, BMI, history of congestive heart failure, medication profile, and polysomnographic features such as: presence of atrial fibrillation, measurement of the circulation time (calculated from the end of a central apnea to the nadir of the resulting desaturation) and interapnea recovery breathing time (calculated from the end of one central apnea to the beginning of the next central apnea) The latter 2 calculations were obtained in stable Stage II sleep when there was a significant aggregation of central apneas, and were calculated by a blinded observer without prior knowledge of the cardiovascular parameters. Cardiovascular systolic function was assessed by the echocardiographic measurement of the ejection fraction of the left ventricle (LVEF). None of the patients were studied at high altitude or were using narcotics at the time of PSG.
Results: Our Seventeen patients demographics include: age (62.8 ±9.7), 15 were males, BMI (32.8 ±8.6), Epworth sleepiness score (13.8 ± 6), (LVEF)(44.5 ± 15.2), CT in patients with LVEF below 40% (42.8 ± 13.6), CT in patients with LVEF above 40% (25.9 ± 7.61), A correlation of the (LV) ejection fraction was performed with CT and IARBT with an ($r = -0.69$, $p < 0.01$) and ($r = -0.43$) respectively. A correlation of the Left Atrium (LA) size was performed with CT with an r: 0.74 ($p < 0.01$) There is a significant inverse correlation between the CT and the left ventricular function and direct correlation with the (LA) diameter.
Conclusion: (CSA) seen in a positive pressure therapy polysomnogram represents a clinical dilemma that has to be addressed during the (PSG). According to our data the measurement of circulation time will help to differentiate among different causes of central apneas and may help to avoid unnecessary escalation of positive pressure and resulting hypocapnia which will facilitate the persistence of (CSR). Further testing of this conclusion in a prospective protocol is warranted

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Self-Reported Habitual Snoring in the Wisconsin Sleep Cohort Study

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Introduction: Epdemiology studies of the correlates and adverse health effects of sleep-disordered breathing commonly rely on self-reported snoring frequency as the key variable. Classification of chronic snoring status based on this one-time measure may introduce error due to the subjective nature of the data as well as possible changes in snoring frequency over time. Limited data indicate that short-term reliability is moderate at best. We investigated the consistency of self-reported snoring frequency over 3-24 months to determine the reliability of habitual snoring status.
Methods: Our sample consisted of 1197 men and women, ages 30-65, enrolled in the Wisconsin Sleep Cohort. Participants completed a mailed questionnaire at baseline that included the following question: "According to what others have told you, please estimate how often you snore". Semi-quantitative response categories were: 1) Never; 2) Rarely-only once or a few times ever; 3) Sometimes-a few nights per month; 4)At least once a week, but pattern may be irregular; 5) Several (3 to 5) nights per week; 6) Every night or almost every night. The same question was asked again at the participant's overnight laboratory study. For this analysis, categories were combined to define snoring status as follows: non-snoring=category 1 or 2, some snoring=category 3 or 4, and habitual snoring=category 5 or 6. The time intervals between the mailed survey and data collected by questionnaire in the laboratory were less than 3 months for 73 participants, 3-6 months for 178 participants, 6-12 months for 379 participants, and 12-24 months for 567 participants.
Results: Of participants reporting habitual snoring at baseline 88%, 84%, 86%, and 86% reported habitual snoring at the 3-, 6-, 12-, and 24-month time intervals. Over 99% (80/81) of the partcipants who were discordant on habitual snoring shifted to the some snoring category at follow-up. The percent concordance, however, for non-snoring was lower, with 36%, 50%, 66%, and 62% of non-snorers also reporting never or rarely snoring at the 3-, 6-, 12-, and 24-month time intervals. Of those discordant on non-snoring, approximately 75% reported some snoring follow-up and approximately 25% reported habitual snoring at follow-up
Conclusion: Habitual snoring status based on self-reported frequency of snoring appears to be a reliable indicator for at least 2 years post survey, with nearly all habitual snorers reporting at least some snoring at any follow-up. The lesser reliability of self-reported non-snoring is likely to be due in part to the expected increase in prevalence of snoring with age, but may also reflect errors in the subjective report.

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Using Psychological Theories of Behavior Change to Predict Treatment Adherence in Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS)

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Introduction: Continuous Positive Airway Pressure (CPAP) is the most commonly used form of treatment for OSAHS. Although treatment is accepted by most patients, nightly use is disappointingly low. Patient-reported barriers to nightly use focus primarily on side effects, such as mask discomfort. Improvements in these areas, however, have produced minimal changes in CPAP use among patients. Psychological theories of behavior change can be applied to the problem of non-adherence to CPAP. Measures derived from the Transtheoretical Model (TTM) and Social Cognitive Theory (SCT) have been shown to predict CPAP adherence over a 1-month period. In the present study, we attempt to replicate

these findings and extend the follow-up period to 3 months.
Methods: Eighty-one consecutive participants, recruited as part of a large-scale clinical trial testing the efficacy of behavioral methods to improve adherence to CPAP, were examined for this study. Participants were included in the study if they were between 25-80 years of age, medically and psychiatrically healthy, diagnosed with OSAHS by overnight polysomnography, judged by their sleep physician to be CPAP responders, and willing to try CPAP as their treatment. Reliable and valid measures of the constructs of readiness, decisional balance (TTM), and self-efficacy (SCT) were administered as part of an extensive assessment battery at baseline (prior to CPAP initiation), and at 3, 6, and 12 months post-CPAP initiation. Two-thirds of participants received additional assessments of the TTM and SCT constructs after 1 and 2 weeks of treatment. Nightly CPAP use was monitored objectively throughout the study using Respironics SmartCard™ technology.
Results: The average age of the sample was 51.5 years (sd 11) and their average RDI was 44 (sd 25). The group included 26 women. TTM and SCT measures taken at baseline did not predict CPAP use at 1 month. Readiness taken after 1 week of CPAP use, however, accounted for 16% of the variance in use at 1-month, after controlling for subjective sleepiness (Epworth Sleepiness Scale). No other measure predicted use at 1 month when taken at this time. Readiness and decisional balance measures taken at 3-months, respectively accounted for 37% and 36% of the variance in use at 3 months, over and above subjective sleepiness. Self-efficacy taken at the same time accounted for 50% of the variance in 3-month use. Any combination of the TTM and SCT measures taken at 3 months accounted for 51 to 54% of the variance in use at 3 months, over and above sleepiness.
Conclusion: The behavior change theories of TTM and SCT strongly predict CPAP adherence in OSAHS, particularly after extended periods of CPAP experience. Consistent with previous findings, these measures do not predict future use when taken at baseline. Thus, some experience with the treatment is required before these measures can provide an adequate reporting of the pros and cons of use and one's readiness and confidence that nightly use can be accomplished.

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Correlates of Depression at Baseline and 3 Months Post-Treatment in Obstructive Sleep Apnea Syndrome

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Introduction: Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS) has several negative daytime consequences, including mood disturbances such as depression. The aim of this study was to examine the correlates of depression at baseline in a clinical sample of OSAHS patients participating in a large scale clinical trial of Continuous Positive Airway Pressure (CPAP) adherence. We also sought to determine the effects of CPAP treatment on depressive symptoms and the correlates of change in depression scores.
Methods: Data on the first fifty-seven patients (mean age 50.3 years, sd 10.8, 18 women) completed through three months from a clinical trial examining treatment adherence in patients with OSAHS were examined. Participants are eligible for the parent study if they are between 25-80 years of age, medically and psychiatrically healthy, diagnosed with moderate to severe OSAHS by overnight polysomnography, judged by their sleep physician to be CPAP responders, and choose CPAP as their treatment. The BDI-II was administered as part of a 3-hour neuropsychological assessment battery at baseline (prior to CPAP initiation), and at 3 months post-CPAP initiation. Three other subjective measures of daytime functioning, the Epworth Sleepiness Scale, the Apathy Evaluation Scale, and Functional Outcomes of Sleep Questionnaire (FOSQ), were also administered at these time points. Objective CPAP adherence was measured by covert monitoring via Respironics SmartCard™ technology and gathered at the three-month follow-up.
Results: At baseline, scores on the BDI-II were significantly correlated with scores on the Apathy Evaluation Scale ($r=.51$, $p<.001$), and total FOSQ score ($r=.57$, $p<.001$). There was a trend level correlation with age at baseline ($r=-.24$, $p<.07$). There was no relationship between BDI-II scores and baseline OSAHS severity (e.g., RDI, arousal index) or subjective sleepiness. At the 3-month follow-up, scores on the depression measure declined significantly overall [$t(56)=5.64$, $p<.001$]. Decrease in BDI-II depression score from baseline to 3 months was significantly correlated with improvements in subjective sleepiness ($r=.51$, $p<.001$), apathy ($r=.51$, $p<.001$), and functional outcomes of sleep ($r=.59$, $p<.001$). Participants with no improvement in BDI-II scores over 3 months used CPAP significantly less at week 12 of the study compared to those whose scores on the BDI-II decreased ($t(47)=-2.1$, $p<.04$). The two groups were similar in baseline apnea severity, subjective sleepiness, and depression.
Conclusion: Subjective reports of various daytime consequences of apnea tend to be related to each other more so than to objective indicators of OSAHS severity. Changes in subjective measures do not reflect objective change in disease state. Poor adherence to treatment may be a risk factor for continued reports of depression after the initiation of CPAP. We are continuing to examine these issues in this large-scale clinical trial of CPAP adherence.

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Prevalence of Cheyne-Stokes Respiration and Obstructive Sleep Apnea in Subjects with Congestive Heart Failure

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Introduction: This study investigates the prevalence of Cheyne-Stokes respiration (CSR) and obstructive sleep apnea (OSA) in subjects with congestive heart failure on an optimal medical regimen.
Methods: 69 consecutive subjects (79% participation rate) were recruited through the Heart Failure Clinic of the Brigham & Womens Hospital. Subjects were included between the ages of 18 and 80, NYHA class II-IV, had CHF secondary to ischemic or idiopathic dilated cardiomyopathy, were clinically stable and had an LVEF ≤40%. Medications included: 88% of subjects on loop diurectics, 35% K-sparing diruectics, 90% ACE inhibitors, 7% ARBs. 65% digoxin, 46% beta blockers, 21% beta and alpha blockers. Subjects underwent in-home overnight screening with the StarDust device (nasal pressure, thoracic excursion [piezo-electric crystal], and pulse oximetry.) CSR was defined as a symmetrical crescendo-decrescendo respiratory pattern with a > 50% difference between peak and nadir pressure or effort, occurring with a 30 to 90-second period. CSR time (as a percentage of total recording time) ≥ 33% was considered positive for CSR. Primary OSA was defined as an AHI ≥ 15 (Chicago criteria) and a CSR time ≤33%. Subjects also underwent laboratory cardiopulmonary exercise testing.
Results: 24 subjects (2 female) had CSR (central apnea index 15.1 [7.7-24]), 45 (5 female) did not (CAI 0.2 [0.0-2.1] $p < .001$). The prevalence

of CSR was 35%. Significant differences between respective groups (CSR vs. no CSR) included NYHA class (71% vs. 29% class III-IV and 40% vs. 60% class II [p = .02]), and peak respiratory exchange ratio (1.13 [.02 SEM] vs. 1.06 [.02 SEM], p = .02). Non-significant differences between the groups included sex, age, BMI, left ventricular ejection fraction, and rate of diabetes. Non-significant differences in exercise testing included peak rate pressure product, physical work capacity, and maximum blood pressure. Predictors of CSR (by multiple logistical regression analysis) included NYHA Class III-IV (odds ratio 3.6, 1.3-10.5 95% CI, p = 0.017), and peak respiratory exchange ratio increase of 0.1 unit (OR 2.0. 1.1-3.8 95% CI, p = .033). 19 subjects (4 females) had primary OSA (AHI 34.3 ±18.4). The prevalence of primary OSA was 28%. 36% of subjects had both a CSR time ≥ 33% and an AHI ≥ 15.
Conclusion: We report a 35% prevalence of CSR and 28% prevalence of primary OSA in this population of subjects with CHF. This CSR prevalence is somewhat lower than in the literature. This is especially surprising given the novel CSR metric we used. We believe the usual practice of reporting the CAI as a surrogate for CSR significantly underestimates the presence of CSR, due to the presence of hypopnea, not apnea, at the nadir of the cycle. Only 20% of our subjects had a CAI ≥ 10. We speculate the decreased prevalence may be due in part to the increased efficacy of newly available CHF medications.

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Complications of Nasal Continuous Positive Airway Pressure Therapy

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Introduction: Therapy with nasal continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA), is reportedly susceptible to several complications. Our sleep center keeps a nurse in charge of following-up patients on CPAP and we have the impression that complications are infrequent. This impression, however, could be biased by the fact that the phone contacts seize the patients out of the medical context and they can forget to mention a problem that may be already solved, besides the sampling bias of reached patients being the successful ones and discontented patients avoiding contact. The aim of this study was to verify the occurrence of complications when individuals are specifically interviewed using a symptom check list.
Methods: We selected a sample of 768 patients to whom CPAP therapy was prescribed from a database currently being contacted annually. Phone calls started on December 1, 2003. Patients, for whom a previous Epworth Sleepiness Scale (ESS) was available, repeated the questionnaire by phone. Patients informed body weight and were requested to answer "yes" or "no" to each one of the problems in the symptom checklist obtained from complications described in the literature and from our patients' reports: 1) skin lesions due to mask abrasion, 2) skin reaction due to allergy, 3) claustrophobia, 4) suffocation, 5) nose bleeding, 6) sneezing, 7) runny nose, 8) stuffy nose, 9) conjunctivitis, 10) facial edema, 11) change of voice, 12) excessive salivation, 13) jaw pain, 14) headache, 15) toothache, 16) chest pain, 17) aerophagia, 18) insomnia, 19) irritability, 20) ear symptoms.
Results: 79 patients had been interviewed until December 13. They were 62 men and 17 women (22%; CI 95% 13-32%). Mean (±SD) age was 63±13 years. 86% had technical or university education. Mean time since patients started to use CPAP was 25±19 months. Mean CPAP was 11±3 cmH2O, ranging from 5 to 20 cmH2O. 16 had abandoned therapy: five abandoned CPAP due to complications, four died due to cancer (3 cases) and stroke, four neglected treatment for considering themselves cured, three did not explain why quit. Pressure (p=0.44) and AHI (p=0.62) did not differ between users and quitters. Among the 63 users, 60 reported using CPAP 7 days a week. Mean hours of use was 6±2 hours, ranging from 2 to 8 hours. Sleepiness measured by the ESS had reduced from 13±5 to 4±6 (p=0.000) from before to present measurement. Body mass index had reduced from 31.1±5.0 to 30.0±4.5 (p=0.02). Dry mouth was the most frequent complication being present in 22 cases (35%; 24-48%). Four cases complained of runny nose (6%; 12-16%), three had ocular discomfort due to leakage in the mask that resolved changing the mask (5%; 1-14%) and one case each (2%; 0.1-10%) complained of skin problems caused by the mask, stuffy nose, aerophagia, irritability, insomnia.
Conclusion: In this partial sample adverse effects of CPAP therapy are surprisingly minor and rare. This may be due to the higher socioeconomic and educational level of the patients who can afford buying a CPAP device in Brazil.

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Interventions To Improve CPAP Compliance In Non-Adherent Obstructive Sleep Apnea Patients

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Introduction: Many OSA patients do not initially adhere to prescribed CPAP therapy. Such patients are often referred to sleep disorders specialists for efforts to improve compliance. Interventions commonly employed include education, mask refitting, and changes to alternative positive pressure modalities, including bi-level therapy. The efficacy of these interventions remains uncertain. We hypothesize that a 2-stage, interventional approach employing standard, problem-directed interventions followed by a trial of bi-level therapy will achieve acceptable compliance in previously non-adherent patients.
Methods: Patients were either referred from the community or contacted directly using sleep laboratory and clinic records. All patients reported less than 4 hours of CPAP usage on a daily basis. As stage 1 interventions, patients were: 1) Educated about OSA and treatment options, 2) Assessed for appropriate mask fit, and offered alternative masks if appropriate, 3) Provided heated humidification to be used with CPAP, and 4) Provided saline nasal washes and nasal corticosteroid therapy for chronic or allergic rhinitis. After their treatment regimen was optimized, they were provided CPAP devices with heated humidifiers and compliance monitors to be used for two weeks. Patients were instructed to return in 14 days for reassessment of adherence.
Results: To date 120 patients (79 male, 41 female) with previously diagnosed OSA and reported non-adherence to CPAP therapy have enrolled in this protocol. Mean age was 52.0 + 12.7 years. Mean BMI was 34.1 + 7.7 kg/m2. Mean baseline apnea/hypopnea index (AHI) was 41.8 + 29.4 events/hr and mean CPAP prescription was 8.9 + 2.3cm H2O. CPAP adherence at enrollment estimated from self-report and run time/compliance meters was 2.1 + 1.1 hours per night. 101 patients (84% of those enrolled, 43 male, 20 female) have returned after 14 days of optimized therapy for compliance reassessment. 37 (37%) had objective meter readings of > 4 hrs/day. Mean daily CPAP use in this compliant group (> 4 hrs/night) was 4.6 + 2.1 hours, while mean daily use in the less compliant group (< 4 hours daily, n = 64) was 1.6 + 1.3 hours (p < 0.05). The 2 groups did not differ in age, gender distribution, BMI, baseline AHI, prescribed level of CPAP, or entry complaints of sleepiness, restless sleep, morning headache, poor mask fit, nasal dryness, or rhinitis.
Conclusion: These results provide a preliminary estimate of the success rate from a problem-directed, comprehensive protocol directed to

improving CPAP compliance in OSA patients previously non-adherent with CPAP therapy. We hope this will provide a benchmark for comparison with other interventions to optimize CPAP compliance. We have not yet identified clinical predictors for successful response to these interventions. We hypothesize that the addition of bi-level positive pressure therapy (stage 2 intervention) will further augment compliance rates in such patients.

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Addition Of Modafinil To Conventional Treatment In Obstructive Sleep Apnea Patients

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Introduction: Obstructive sleep apnea (OSA) patients may experience excessive daytime sleepiness (EDS) despite treatment with conventional modalities such as continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) or special dental devices. Modafinil improves EDS in narcoleptics, and in a few short-term trials it has had similar success for up to 12-weeks in OSA patients with EDS. The aim of this study is to assess the long-term response to modafinil in OSA patients who continue to have EDS despite conventional treatment.
Methods: We included patients on modafinil for EDS despite conventional treatment for polysomnographically proven OSA. Epworth sleepiness scale (ESS) scores at the diagnosis of OSA and after treatment with conventional modalities were obtained from the patients records. A telephone survey was preformed which included questions about patients demographics, modafinil treatment (dosage, duration, side effects, subjective change in EDS with treatment), current ESS on modafinil, and type of ongoing conventional treatment for OSA as well as patient compliance with this treatment. Response to modafinil treatment was defined as a reduction in ESS score by at least four.
Results: The sample included 22 patients (58% males and 42% females), with a mean age of 53.9 ± 7.0 years. Nine subjects were on treatment with CPAP, eight with BiPAP and one with a dental device. At the time of the survey, four patients were not using any conventional treatment. The average dose of modafinil was 227.3 mg QD (range 100-800) and the average duration of treatment was 17 weeks (range 1-40). No significant side effects were documented. The mean ESS score was 15.9 (SD ±4.5) at diagnosis, 13.6 (SD ±5.6) after treatment with conventional modalities, and 8.9 (SD ±5.1) after treatment with modafinil. There was no statistical difference between the ESS scores before and after conventional treatment (mean difference -0.94; p=0.23 paired t-test); however, the change in ESS score after treatment with modafinil was significant (mean difference -4.68; p=0.003 paired t-test). The improvement in ESS score was similar whether patients were on modafinil for more than or less than 12 weeks (p=0.82 independent sample t-test). On univariate analysis, factors associated with response to modafinil were: higher ESS at diagnosis (Pearson r=0.63; p= 0.007), higher ESS while on conventional therapy (Pearson r=0.65; p=0.001) and male sex (Pearson r=0.46; p=0.03). However, on multivariate analysis a high ESS at diagnosis of OSA and increasing age correlated with response to modafinil (multivariable r=0.78; p=0.002).
Conclusion: Modafinil is a safe and effective adjunct therapy for EDS in patients with OSA receiving adequate conventional therapy. In our study population, treatment with modafinil was more likely to be effective in the elderly and those with high ESS scores at the time of diagnosis of OSA, and the effect persisted irrespective of duration of treatment.

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CPAP Use and Acceptance in Patients with Insomnia and Obstructive Sleep Apnea

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Introduction: Some OSA patients also complain of symptoms of insomnia (i.e., sleep onset insomnia, sleep maintenance insomnia). It would appear that these patients present special difficulties in CPAP treatment of OSA. Anecdotal evidence suggests that patients with insomnia and OSA have decreased compliance and poor acceptance of CPAP.
Methods: We performed a retrospective consecutive case series of patients with a diagnosis of OSA and a CPAP trial seen at the Mayo Clinic Rochester Sleep Disorder Center from Jan 1 to Feb 24, 1999. Of 207 patients, 23 had insomnia diagnosed following consultation with a certified sleep disorders specialist. All patients were given a CPAP prescription and 19 filled the prescription. These patients were contacted for follow up using a questionnaire that included current CPAP compliance, total sleep time, time to sleep onset, and awakenings.
Results: Fifteen of 19 patients responded. Average length of follow-up was 46 months. Fourteen patients (93%) continued to use CPAP for an average of 5.5 hrs/night (4.5-8 hrs); all used it 7 nights a week. One patient was not currently using CPAP. CPAP compliant patients reported sleep onset time of 18.2 +/- 8.5 min using CPAP compared with 42.1 +/- 18.4 min before CPAP use. Ten of 14 CPAP compliant patients reported decreased nocturnal awakenings since starting CPAP.
Conclusion: Acceptance and compliance with. CPAP appear to be satisfactory in patients with insomnia and OSA. Insomnia patients did not find it harder to fall asleep using CPAP than when not using it, in fact, they appeared to have a decrease in time to sleep onset and decreased nocturnal awakenings with CPAP. This suggests that the apnea may have been causing the initial and maintenance insomnia.

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Unsupervised Home Auto-titration CPAP Titration Does not Supplant Supervised NPSG-monitored CPAP Titration for Patients Who Have Had an Incomplete CPAP titration as part of a Split-Night NPSG

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Introduction: Severe obstructive sleep apnea can be diagnosed is a few hours and initiating and titrating CPAP on the night of the diagnostic study may enable earlier treatment initiation, save health-care resources and increase the availability of the sleep laboratory for other diagnostic testing. There is concern that the optimal CPAP level may not be determined if insufficient sleep time is recorded on CPAP, but evidence to support such concern is limited. Home auto-titration might obviate the need for a follow-up PSG monitored CPAP titration for individuals who do not appear to have been successfully treated with CPAP on the night of their initial study.
Methods: Subjects with confirmed, newly diagnosed severe obstructive sleep apneas syndrom who met our laboratory criteria for a CPAP titration (40 OA and or OH with 4 percent desaturation, during two or more hours of PSG-monitored sleep) were seen in follow up by the PI (hhs). Each patient was given an opportunity to try different nasal and oral CPAP masks with CPAP and chose one they felt they would be most comfortable with at home. Each patient was initially treated for two weeks with an auto-titrating CPAP appliance (AutoSet-T ResMed). Patient use, pressure profile and mask leak data were reviewed and each

patient seen in follow up
Results: Nine consecutive male patients were enrolled in this study. Five patients did poorly. These individuals used CPAP greater than 25 percent of prescribed days and greater than 2 hrs per night. Their CPAP titrations were noteworthy in two respects: failure to reduce the RDI by less than 67percent and failure to sleep for at least 2 hrs. Four individuals did well on CPAP. They were similar in age (average 49, STD 13) RDI (av. 60, 19 STD), and BMI (33, 6 STD). Sleep on CPAP average, 2.4 hr (1.4 STD). The final CPAP level was 14 (3.6 STD). Each used the AutoSet-t most days (84 percent average 15.5 days). CPAP levels on the AutoSet were similar (13 2.1 STD). Mask leak problems were identified and addressed by adjusting the mask fit in two individuals. All of the latter patients were compliant at three months follow up. 80 per cent (4 of 5) patients with inadequate CPAP titrations wereeither not using CPAP at all or are poorly compliant based on follow up auto-CPAP titration monitoring, three months post-test. The individual who has been compliant on CPAP has had a full night CPAP-PSG titration as well as several auto-CPAP titrations.
Conclusion: A technically adequate split night protocol defined as successful elimination of greater than 2/3 obstructive events monitored over greater than 2 hours of PSG-confirmed sleep predicts successful treatment of severe obstructive sleep apnea with CPAP. A split night study failing to meet this standard has identified patients who are likely to have difficulty with CPAP. Home auto-titration is unlikely to obviate the need for a full night devoted to CPAP titration for such individuals. Such premature initiation of treatment may even diminish long term compliance. Such individuals should be evaluated urgently with a supervised full night CPAP titration after mask fitting issues, medically treatable causes of upper airway obstruction, and patient desensitization have been addressed.

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Continuous Positive Airway Pressure Adherence Among Veterans with and without Posttraumatic Stress Disorder

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Introduction: Recent research has identified higher rates of sleep-disordered breathing among individuals with a diagnosis of posttraumatic stress disorder (PTSD). While continuous positive airway pressure (CPAP) therapy has been shown to improve both insomnia and psychiatric symptomatology in individuals with PTSD, research has not been directed toward CPAP adherence in this subgroup of patients. The aim of the present investigation was to determine if individuals with PTSD have lower adherence when compared to veterans without a comorbid PTSD diagnosis, and to identify factors associated with adherence/non-adherence to CPAP treatment.
Methods: Participants were recruited at the time of their follow-up sleep clinic appointment and asked to complete the following self-report measures: Purdue PTSD Scale-Revised, Epworth Sleepiness Scale, Profile of Mood States (POMS), Multidimensional Health Locus of Control Form, CPAP Follow-up Questionnaire and a sleep diary. The total sample of 67 participants was divided into two groups: 27 patients with PTSD, and 40 patients without a PTSD diagnosis (NPTSD) prescribed CPAP for the treatment of sleep-disordered breathing. Objective data concerning CPAP use were downloaded from each patient's CPAP unit.
Results: PTSD patients demonstrated significantly more mood and anxiety symptoms compared to NPTSD patients on all of the POMS scales ($t = -6.29$ to 2.44; all $p < .02$), as well as on self-reported anxiety associated with CPAP use ($z = -3.72$, $p < .001$). The two groups did not differ on objective measures of CPAP use. CPAP adherence, defined as hours of CPAP use divided by self-reported total bedtime, was 54% for the entire group for the 28-day period prior to participation in the study. Patients reported more hours of CPAP use per night ($t = -4.07$, $p < .001$) and more nights of use ($t = -7.05$, $p < .001$) than verified by objective measures of CPAP use. Objective measures of CPAP use were analyzed to subdivide the participants into two groups: CPAP-adherent patients ($n = 38$, mean % use = 86.3 ± 14.8) and CPAP non-adherent patients ($n = 29$, mean % use = 11.4 ± 14.4). Group comparisons on self-report measures of factors interfering with CPAP use revealed non-adherent patients reported more problems using CPAP due to anxiety than CPAP-adherent patients ($z = -2.23$, $p < .03$). A logistic regression analysis identified that self-report of anxiety associated with CPAP use is a significant predictor of group membership, accounting for 9.6% of the variance.
Conclusion: The results of this investigation support previously reported observations of self-report bias in CPAP users, as the sample overestimated their adherence with treatment when self-report was compared with objective data of CPAP use. Anxiety was found to be a significant factor limiting patient adherence with CPAP therapy, regardless of a current diagnosis of PTSD. The results suggest that interventions addressing anxiety-related symptoms interfering with acceptance and adherence are important for improving outcomes for patients with sleep-disordered breathing prescribed CPAP therapy.

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Comparison of Compliance with Proportional Positive Airway Pressure (C-Flex) to Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea

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Introduction: Despite nearly 100% efficacy as a treatment for obstructive sleep apnea (OSA), continuous positive airway pressure (CPAP) compliance is known to be 40% to 70%. The sensation of being unable to fully exhale against CPAP is a frequent complaint of non-compliant patients. A proportional pressure assist device (C-Flex) is known to provide a base pressure to prevent pharyngeal collapse, while decreasing cumulative expiratory pressure exposure compared to CPAP.
Methods: Randomized, single-blinded, controlled trial of 4 week course of C-Flex versus CPAP. Sixteen, newly diagnosed, adult OSA patients with an apnea-hypopnea index (AHI) > 15, without REM-related or supine positional OSA with an uncomplicated laboratory CPAP titration study. Subjects self-adjusted expiratory pressure relief with C-Flex at one of three settings but remained on the laboratory determined inspiratory pressure that was used for CPAP. Compliance was monitored objectively with Smart Card Technology. Treatment outcomes were compared with the Functional Outcomes of Sleep Questionnaire (FOSQ) and the Epworth Sleepiness Scale (ESS). Results were compared using ANOVAs and linear mixed effects.
Results: There was a trend for increased compliance with C-Flex compared to CPAP for most of the parameters measured, however none of the compliance parameter differences were statistically significant. Of note, hours of nightly usage trended higher for C-Flex compared to CPAP (5.9 + 1.9 vs 5.3 + 4.7, p=.09). The FOSQ improved for C-Flex compared to baseline (-14.8 + 24, p=.04) but not for CPAP, although for both treatments compared to each other, there was no difference. The ESS improved from baseline with both treatments.
Conclusion: After four weeks, C-Flex did not demonstrate any compliance benefits over CPAP for newly diagnosed OSA patients. However, all the compliance parameters trended higher for C-Flex compared to CPAP, suggesting that this study may have been under-powered to detect a difference between the treatment arms.

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Significant Improvement of Cheyne-Stokes Respiration Induced by REM sleep

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Introduction: Cheyne-Stokes respiration (CSR) is one of a variety of sleep related breathing abnormalities that occur during sleep in patients with congestive heart failure. Its presence adversely affects their prognosis. Because of the frequency of respiratory events and associated sleep fragmentation, patients with CST often fail to progress to deeper sleep stages. A sleep stage relationship of CSR has not been well defined. We report our experience of 2 cases in which CSR disappeared during REM sleep, and suggest a theory behind this phenomenon.
Methods: We performed a retrospective review of our database of patients to find those with predominantly central sleep apnea (CSA) in their CPAP polysomnograms (PSG), specifically patients in whom their obstructive apnea disappear and central apnea remain.. Patients were then selected if they had significant improvement of CSR by any sleep stage or position. Each of these patients sleep studies were thoroughly reviewed along with their medical records for demographic data and sleep parameters before and while on CPAP. To address known factors reported to affect CSR, these sleep studies were performed in our low altitude location and none of the patients were exposed to opioids.
Results: Our database consist of 35 patients with CSA, 2 of those patients met the selection criteria and had REM related improvement of CSR. Both were male with a mean age, BMI, and Epworth sleepiness score of 59.5 years, 44.4kg/m2, and 16 respectively. On those initial sleep studies both had a coexistent moderate obstructive and central sleep apnea with CSR. They underwent a positive pressure titration PSG. On these studies, as the obstructive events cleared they exhibited exacerbations of CSR in NREM sleep, however, the CSR substantially improved in each of the 3 REM episodes observed. Mean Central REM RDI (on CPAP) was 1.6 [3.2 and zero], Mean central non-REM RDI (on CPAP) was 42 on escalating CPAP pressure to control the obstructive events. Mean sleep stage distribution (on CPAP) [%] was: Light Sleep (Stage I+II) 32%, Delta Sleep (Stage III+IV) 4.2%, and REM sleep 16.5% [12.5 - 9%]. Clinically, both patients had severe mitral regurgitation and mild to moderately reduced LV function. The improvement of CSR during REM sleep had been described related to sleep position, opioid therapy and high altitude, none of these situations can explain our findings on these two cases.
Conclusion: Patients who have pre-existing central and obstructive sleep apnea who undergo CPAP titration often have deeper sleep stages, especially REM. This is in contrast to untreated CSR patients who have a very small amount of REM sleep (<8%) due to fragmentation of sleep by respiratory events. The increased REM % with treatment has allowed us to see consistent REM, to determine the effect of REM sleep on CSR. We postulate that the substantial improvement of CSR in REM sleep might be explained by the known effect of REM producing some degree of hypoventilation which may be eliminating hypocapnia that is a prerequisite to develop sustained periodic breathing in sleep.

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Characteristics of Symptoms and Background Variables in Familial Obstructive Sleep Apnea-hypopnea Syndrome

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Introduction: Many studies have indicated that obstructive sleep apnea-hypopnea syndrome (OSAHS) is much more prevalent in first-degree relatives of patients with the disorder than general population. However, both clinical characteristics of familial OSAHS and causative factor for the aggregated occurrence of the disorder in families have not been well identified. In order to clarify this issue, we made a systematic study about clinical characteristics and background factors on adult familial OSAHS patients.
Methods: Familially occurred OSAHS patients (n= 33 in 14 families, M: F=27: 6, average age; 38.3 years, apnea hypopnea-index; 32.4+/-9.9/hour) and the age, sex and apnea-hypopnea index (AHI) matched non-familial OSAHS patients (n=32, M: F=28: 4, average age; 37.6 years, AHI; 32.4+/-9.3) were subjected in this study. All the subject OSAHS patients did not have any specific diseases causative for upper airway narrowing and showed normal finding on hypercapnic response study in the daytime. Between the above two groups, polysomnographic(PSG) variables, severity of daytime sleepiness measured with Epworth Sleepiness Scale (ESS), percentage of the patients with cardiovascular disease, clinical histories interviewed from their family members and background variables including as body mass index (BMI), smoking history and daily alcohol consumption were compared. Moreover, standard cephalometric variables were compared among familial OSAHS group, non-familial group, and healthy control group (n=33, M: F=29: 4, average age; 37.8 years).
Results: Both oxygen desaturation variables and sleep structure variables on PSG did not differ between the two OSAHS groups. However, the percentage of the subjects with hypertension was significantly higher in the non-familial group than the familial OSAHS group despite no difference in ESS points between the two groups. With respect to the clinical histories, both the onset age of habitual snoring and the first witnessed age of sleep apnea were significantly younger in the familial OSAHS group than the non-familial group. Among background factors, BMI was significantly lower in the familial OSAHS group than the non-familial group. Regarding cephalometric variables, both PAS and SNB were significantly smaller in the familial OSAHS group than those in the other two groups. On the other hand, MPH was equally larger in the two OSAHS groups than that in control subjects, and the other parameters did not differ among the subject three groups.
Conclusion: The most interesting finding in our result was that the onset age of OSAHS was younger in the familial cases than the non-familial cases. This finding strongly suggests the acceleration of the appearance of the disorder in genetically predisposed subjects, and minor anomaly of craniofacial morphology manifested on some cephalometric variables was thought to act as a main causative factor. The prevalence of hypertension was lower in the familial OSAHS group than the non-familial group despite no differences in PSG variables between the two groups. Taken these findings together, existence of obesity was thought to contribute not to the familial occurrence of OSAHS but to the appearance of hypertension.

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Quantitative Upper Airway Digital Morphometrics And The Risk For Obstructive Sleep Apnea

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Introduction: Recent imaging studies have demonstrated strong correlations with the size of upper airway soft tissue structures and the risk for obstructive sleep apnea. Specifically, enlargement of the tongue, lateral pharyngeal walls, tonsils, uvula, total pharyngeal soft tissue, and reduction in the length of the mandible have all been shown to be important structures in the pathogenesis of OSA. Morphometric studies, which do not need sophisticated imaging technology and are much less expensive, have also suggested that examination of soft tissue structures of the pharynx are important in the pathogenesis of sleep apnea. However, previous morphometric studies have not objectively quantified upper airway structures with digital imaging techniques. Thus, our study goals were to examine pharyngeal soft tissue structures using quantitative digital morphometrics in order to determine the risk factors associated with obstructive sleep apnea utilizing a case control design. We hypothesized that we could utilize quantitative digital morphometrics of the pharynx to accurately predict who is at risk for sleep apnea.
Methods: Five normal subjects (RDI<5) and 5 sleep apnea subjects (RDI>10) underwent digital morphometric examination with a novel laser ruler device. The laser ruler device that we have developed and validated allows for quantitative measurements intra and extra-orally by projecting two laser beams with a known inter-laser distance. Digital photographs were obtained using the laser ruler device while subjects were instructed to follow standardized instructions (i.e., 'Say Ah for 5 second', 'Take a deep breath out and hold it'). Photographs with and without a tongue depressor were obtained. All subjects subsequently underwent polysomnography to determine the RDI. The sizes of the uvula, airway, pharyngeal arch, pharyngeal lateral walls, tongue and tonsils were measured using image analysis software.
Results: All of the subjects with sleep apnea had upper airways that were not visible upon physical examination without an intervention (phonation or tongue depressor.) Only the control subjects had visible upper airways without phonation or use of a tongue depressor. Moreover, we found a significant difference (P=0.03) between the mean lateral wall width between the cases (2.18 cm, SD=0.61) and the controls (1.48 cm, SD=0.25) when phonating. The mean tongue width for apneics (5.76, SD=0.70) was larger than the controls (5.01 cm, SD=0.57) but did not reach statistical significance (P=0.09).
Conclusion: We have demonstrated that digital morphometrics can be used to quantitatively measure oral soft tissue structures. This analysis supports previous imaging research documenting significant morphometric differences between patients with sleep apnea subjects and normal controls. Our initial data has demonstrated that the lateral pharyngeal were larger in patients with obstructive sleep apnea than controls.

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Genioglossal EMG Activation During Sleep has Different Effects on Upper Airway Airflow in Obstructive Apnea vs. Normal Subjects.

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Introduction: Neuromuscular responses to upper airway obstruction (UAO) help maintain upper airway patency in normal individuals during sleep. Obstructive sleep apnea (OSA) is thought to occur secondary to disturbances in upper airway neuromuscular control that may result from decreased neural activity or diminished mechanical efficiency of upper airway muscles. We hypothesized that: (a) normal subjects would demonstrate increases in maximal inspiration (VImax) as neural activity increased in response to UAO, (b) in contrast, neuromuscular responses to UAO in OSA would either be diminished, or would not be associated with an increase in VImax.
Methods: We examined the relationship between VImax and genioglossal EMG (EMGgg) response to UAO in 8 normal and 7 OSA subjects during stage II NREM sleep. UAO was elicited by lowering nasal pressure (PN). Nasal airflow was assessed acutely, before an EMGgg response occurred (passive state), and after recruitment of neural activity during sustained periods of UAO with EMGgg activation (active state).
Results: Normal subjects demonstrated consistent increases in both EMGgg and VImax during the active compared to the passive state (p=<0.05). In contrast, OSA subjects demonstrated heterogeneous responses to UAO, consisting of either inverse (n=2) or direct (n=3) relationships between EMGgg and VImax, or no EMGgg activation (n=2).
Conclusion: UAO may be prevented by upper airway neuromuscular responses in normal subjects but not OSA patients. Our findings imply that disturbances in neuromuscular control may lead to UAO in OSA, and that these disturbances are caused by diminished neural activation and/or mechanical efficiency of upper airway muscles.

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Pressure Derived From Auto-CPAP Compared to Standard Laboratory Titration in Newly Diagnosed Sleep Apnea Patients

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Introduction: Practice standards, guidelines, and options were recently published in an American Academy of Sleep Medicine Practice Parameter Report (2002). One area noted for noted for its paucity of data concerns using unattended automatic positive airway pressure (APAP) in CPAP-naive patients for initial determination of pressure requirements for either: 1) fixed CPAP use or 2) continued APAP treatment. We report here a randomized, controlled trial designed to compare the pressure level derived from APAP in CPAP-naive patients with obstructive sleep apnea (OSA) to the pressure derived by standard pressure titration by sleep technician.
Methods: This was a prospective, randomized crossover equivalency study comparing one night on the AutoSet Spirit APAP (ResMed, Inc., Poway, CA) device to standard manual split-night titration in patients with previously undiagnosed OSA. Thirty-two consecutive patients clinically suspected of having OSA were screened, of which 30 patients were randomized to receive either manual or APAP titration on one night followed by the other titration method on a second night. Patients randomized to APAP wore the device for one night in the sleep center, with no sleep technician intervention to address mask problems and minimal intervention to address EEG lead problems. APAP was set to a range from 4 to 20 cmH2O and settling time was 5 minutes. The APAP 95th centile was obtained from Autoset download and verified by manual scoring. Those randomized to manual titration had pressure started at 5 cmH2O, with pressure being raised in increments of 3 cmH2O until the

AHI was decreased to less than 3 per hour and the number of snoring and respiratory-related arousals were minimized. Once this was achieved, pressure could be decreased by 1 cmH2O, but only to 1 cmH2O above the last ineffective pressure. Technologists conducting manual titration were blind to APAP pressure results in cases where they had been determined previously.
Results: 24 men and 6 women participated. The sample age (mean ± SD) was 47.4±12.7 years and ranged from 21 to 68. The 95th centile pressure derived from APAP group (10.49±2.3; range: 6.2–18.4) did not differ from that derived from manual titration (10.47±2.4; range: 7–16) for the entire sample (t=.05; p=0.962). The mean difference in pressure between the groups was 0.02±2.29 (range: -3.6 to 4.8). There was no order effect (F=2.0; p=0.168).
Conclusion: In this prospective, randomized crossover study, no significant difference in pressure level was found between the pressures derived from the AutoSet Spirit compared to manual titration. This study provides support for the determination of positive airway pressure requirements for OSA patients through the use of an unattended APAP device. Doing so can facilitate CPAP care delivery and reduce costs. Future studies will need to examine how well pressure determination by APAP affects patient outcomes at follow-up.

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Automated Versus Visual Determination of Effective Nasal Pressure During Clinical CPAP Studies

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Introduction: AutoCPAP devices are widely used to predict the effective therapeutic nasal pressure (Peff) in apneic patients. The determination of Peff is based on the statistical analysis of pressure-over-time (Pmean/P90) data. However, recent studies demonstrated a significant difference in the estimate of Peff between study nights and different AutoCPAP devices, implying that Pmean and P90 are inappropriate to determine Peff. In contrast, measuring quantitative airflow in response to step increases in nasal pressure has been shown to be best suited to determine Peff in the clinical setting. However, no attempt has been made to automate the step increases in CPAP pressure. We hypothesize that an automated stepwise titration protocol allows to titrate CPAP in the clinical setting and that the airflow response to these automated nasal pressure increases would allow to define effective therapeutic nasal pressure levels.
Methods: We developed an automated CPAP titration algorithm (Magellan AutoCPAP, Resmed/MAP, Germany) that utilizes quantitative pre-calibrated airflow signal to detect the respiratory pattern and the presence of inspiratory airflow limitation. The algorithm increased nasal pressure in response to inspiratory airflow limitation and apneas. In addition, a delay time of 10 minutes at which the algorithm paused was implemented to imitate a standard clinical titration protocol. In 14 apneic patients, age 51.1SD(12.0) years, BMI 35.1SD(8.1) kg/m2, RDI 49.0SD(16.1), we examined the response of the Magellan auto-titration algorithm to sleep related breathing disorders and compared the titration pressure with the determination of Peff by visual analysis of the inspiratory airflow at each nasal pressure level.
Results: The stepwise automatically adjusted effective CPAP pressure was established in 60.1 (SE) 16.1 minutes. The effective automatically adjusted CPAP pressure was 7.4 SD 0.7 cmH2O and did not differ from Peff as defined by the visual analysis of the airflow signal (7.6 SE 0.7 cmH2O). Moreover, while 11 patients had identical Peff in both the automated and visual determination of Peff, three patients demonstrated a difference that was clinically insignificant (1 cm H2O) in 2 patients and significant lower (3 cmH2O) in one.
Conclusion: The Magellan auto-titration algorithm replicates standard CPAP titration protocols and effectively adjusts automatically the effective nasal pressure. Our results imply that the Magellan auto-titration algorithm can be implemented in clinical routine for standard CPAP titration.

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Epworth Sleepiness Scale: Patient versus Partner Usefulness in Clinic and Lab

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Introduction: The Epworth Sleepiness Scale (ESS) is a subject of debate in the literature with respect to 1) its usefulness in predicting sleep disordered breathing (SDB) measured by polysomnography (PSG), and 2) the value of a proxy measure of the patient's ESS as reported by a household partner. The purpose of this study is to determine 1) if the patient's ESS is correlated with sleep disordered breathing, 2) if the patient's ESS is correlated with the household partner's report of the patient's ESS, and 3) the cost/benefit involved in obtaining a proxy ESS.
Methods: During the course of three months, all patients entering a university-based sleep center were given an ESS and an ESS for their household partners to be completed during their appointment. The household partners of the patients who came to their appointment alone were interviewed by phone at a later time. Two groups of respondents were defined: 1) patient-only (PtESS): ESS with PSG following within 3 months, 2) patient-partner pair (PtESS/PnrESS): patient completed ESS prior to PSG and household partner completed ESS assessing the patient's function within 3 months of the patient's PSG. PSG measures AHI and RDI were defined by current Medicare criteria of full apnea or hypopnea with 4% desaturation. Spearman correlation was used to compare 1) PtESS to PSG measures of SDB and 2) PtESS with PnrESS. Student's T was used to compare the means of PtESS and PnrESS. The financial cost involved in obtaining a PnrESS from those who were not available in clinic was estimated based on the time required to reach the partner by phone at $20/hour.
Results: Questionnaires were collected from 171 patients. 15% of patients had a household partner who accompanied them to their appointment. 67% of patients had a household partner but came alone to their appointment. 18% lived alone. 37 patients and partners satisfied the patient-partner criteria while 88 patients satisfied the patient-only criteria. PtESS was correlated with RDI (+0.303 p=0.0045), AHI (+0.323 p=0.0024), and O2 minimum (- 0.313 p=0.003). PtESS was not correlated with Sleep Maintenance %, wake/arousal index, % time less than 90% O2, or EtCO2 maximum. PtESS was correlated to PnrESS (+0.371 p=0.0237). The mean PtESS (12.15, SD: 6.28) and mean PnrESS (9.283, SD: 5.414) were not different by Student's T test. The average cost to obtain PnrESS during clinic is negligible, at home was 0.5 hour, $10.
Conclusion: In this population PtESS is correlated with PSG measures of OSA and thus could be useful in prioritizing patients to undergo PSG. Since PtESS is correlated with PnrESS, PnrESS could be useful to prioritize patients when no PtESS is available. However, obtaining this information from the partner at home, which may take weeks, may render the partners assessment irrelevant for clinical decision making. PnrESS is cost/effective as a proxy measure only if the patient is unable to complete the ESS and the partner is available during the office visit.

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Preferred Sleep Position in Subjects with Obstructive Sleep Apnea Syndrome.

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Introduction: The influence of body position on the occurrence of respiratory events during sleep is well recognized and increased numbers of respiratory events occur when the supine position is assumed. The purpose of this study is to investigate the preferred sleep position in subjects with obstructive sleep apnea syndrome (OSAS) at the time of the diagnosis.
Methods: All subjects presenting to the Cleveland Clinic Sleep Disorders Center complete a questionnaire addressing sleep habits. One of the items ascertained is preferred sleep position (side, back, prone). We compared preferred sleep position in subjects completing the questionnaire from May to December 2003. We excluded subjects in whom OSAS had previously been diagnosed and those who did not choose a single position on the questionnaire. OSAS subjects were subdivided into mild (n= 104), moderate (n= 56), and severe (n= 43) disease.
Results: 203 with OSAS (86 Females, and 117 males) were included. Their preferred sleep position was compared to 26 controls without sleep-disordered breathing (22 females and 4 males). The age of OSAS subjects was 49.5 with a range of 14-83 years. Preferred Position (%) Control Mild OSAS Moderate OSAS Severe OSAS Side 69.2% 77% 78.6% 72% Back 15.4% 10.5% 12.5% 14% Prone 15.4% 12.5% 8.9% 14%
Conclusion: Sleeping on the side is preferred by most of patients regardless of having apnea or not and few prefer the back position. However, whether patients spend the majority of sleep time in their preferred position is unknown. These results are may have implications when educating patients with OSAS about positional therapy.

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Respiratory Disturbances During Sleep in Otherwise Healthy Individuals

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Introduction: Objectives (1) To define the frequency of respiratory disturbances during sleep in otherwise completely healthy individuals using current techniques and criteria; and (2) to determine how the frequency of respiratory disturbances during sleep changes with age and gender. Background The prevalence of respiratory abnormalities during sleep has been extensively studied in general population and various disease states. However, there have been very few studies in completely healthy individuals where pre-existing diseases and medications were excluded. Additionally, most were performed prior to the current recommendations on scoring of respiratory events (AASM taskforce 'Chicago criteria') and many have not utilized recent more sensitive techniques. Moreover, the threshold for defining abnormality has varied widely, partly due to the poor association between respiratory disturbance frequency and symptoms. Therefore, in an effort to help define normality, we report the frequency of respiratory disturbance during sleep in completely healthy individuals using current techniques and criteria and across a wide age range in both genders.
Methods: 106 individuals (71 men) were screened for chronic medical or psychiatric illness as well as for substance abuse. Their healthy status was confirmed by extensive questionnaires, physical examination, electrocardiography, laboratory testing with chemistry profiles, liver function tests, complete blood count, and urinalysis, and questionnaires for sleep disorder symptoms, including the Epworth Sleepiness Scale (ESS) and presence or absence of snoring. Subjects who were obese (BMI>30) or taking medications were excluded. Subjects then underwent full nocturnal polysomnography with standard techniques including sleep stages (4 electroencephalograms, 2 electrooculograms, submental electromyogram), arterial oxyhemoglobin saturation (pulse-oximeter), airflow (snoring microphone, nasal pressure transducer, oronasal thermistors), abdominal and thoracic breathing movement (inductance plethysmography). Apneas and hypopneas were scored visually by using the 'Chicago criteria', yielding an obstructive apnea index (OAI) and an apnea+hypopnea index (AHI). Subjects were categorized by gender and age (younger <55; older >55) and compared using the Mann-Whitney U tests.
Results: In men and women there was a three to fivefold increase in the median AHI above age 55 (younger men = 4; older men = 14.5; $p<0.00000002$; younger women = 2; older women = 11; $p<0.005$). The upper quartile ranges for younger women, older women, younger men, and older men were, respectively 4, 19, 6, and 33. The difference between genders was significant only in the older groups. In men median OAI was greatly increased in older men (0 vs. 6, $p=0.003$), but not different between younger an older women. There was no difference in median ESS scores between the 4 groups (overall median = 3/24). There was a slight increase in body mass index between younger and older groups, BMI being higher by 2 units in the older men and women (overall median=24).
Conclusion: In otherwise completely healthy individuals AHI increases dramatically with age. The most vulnerable population is older males in whom 50% have an AHI >15 using current techniques and scoring criteria. This increase may reflect a normal aging process, thus the interpretation of abnormal breathing during sleep should be adjusted by age and gender.

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Severity Of Sleep-Related Breathing Disorders Correlates With Severity Of Gastroesophageal Reflux Disease In Patients With Heartburn And Sleep Abnormalities

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Introduction: Background and Aims: The association of sleep-related breathing disorders (SRBD) and gastroesophageal reflux disease (GERD) has been suggested in several studies. Although the prevalence of GERD in SRBD ranges from 53 to 76%, the nature and mechanism(s) of their relationship are still unknown. The purpose of this study was to evaluate if the severity of the sleep related breathing disorder correlates with the severity of the gastroesophageal reflux in patients with clinical symptoms of both conditions.
Methods: Methods: Patients with GERD and SRBD symptoms, such as heartburn, regurgitation, snoring, witnessed apnea and excessive daytime sleepiness had portable polysomnography and 24-h esophageal pH monitoring off medications. Gastroesophageal Reflux severity was indicated by DeMeester Criteria (J Clin Gastroenterol,1986). Sleep breathing disorder severity was based on apnea/hypopnea Index. Correlation was made using the Pearson Correlation Method.
Results: Results: 24 patients had pH and sleep study (mean age: 53.2(14) years; mean BMI: 29.9 (14.2) kg/m2; mean RDI: 16.6 (20.2) events/h; mean DeMeester Score : 40.1(32.5), mean % of time with pH <4: 8 (6.7) and mean lowest oxygen saturation: 84.2% (8.8). The correlation between RDI and pH score was .5 ($p < .05$) and the correlation between AHI and % of time pH was < 4 was .5 ($p < .05$). Analysis of acid reflux and respiratory events (10 subjects): 347 reflux events analyzed, 322 occurred during wakefulness and 25 occurred during sleep. All sleep events were associated with arousals (7 were preceded and 4 were followed by arousals). There was no significant association with

time of reflux and respiratory events and only 2 nocturnal events occurred after a respiratory event (hypopnea).
Conclusion: Conclusion: In patients with sleep complaints related to obstructive sleep apnea and gastroesophageal reflux, the severity of the sleep breathing disorder is correlated with the GER severity. It has been suggested that the increase in nocturnal clearance time could be a possible explanation for the increase in acid exposure and consequently increase in GER severity, but the almost absence of nocturnal events in the subgroup of patients studied did not confirm this hypothesis. Other possible mechanisms are the impact of increased respiratory effort on LES function. More studies are necessary to establish a causal relationship between the two entities, if one exists, and elucidate the mechanism for the severity correlation between both disorders.

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Relavence Of Body Mass Index And Body Position In Patients Who Have A Higher NREM RDI Than REM RDI

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Introduction: Obstructive sleep apnea may be affected by body mass index, sleep position and may vary in different stages of sleep. OSA has been proven to be worse in REM than in NREM.No one has ever looked at whether body mass index and body position determine whether patients have a higher Non REM RDI than REM RDI.
Methods: We looked at the polysomnographic data of 50 consecutive patients with obstructive sleep apnea. We then determined whether the patients had a higher NREM RDI than REM RDI. We then correlated body mass index and body position in these patients versus those whose REM RDI was higher than NREM RDI.
Results: Body mass index seems to have no effect on whether patients had a higher RDI in NREM than REM. The number of patients who spend time in supine versus nonsupine positions did not seem to influence whether patients had an higher RDI in NREM than REM sleep.
Conclusion: Body mass index and body position donot influence whether patients higher NREM RDI than REM RDI.

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Disturbed Respiratory Events Associated with Arousals and Minimal Arterial Oxygen Desaturations are Associated with Daytime Sleepiness

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Introduction: Apneas and hypopneas with >/=4% arterial O2 desaturations have been associated with daytime sleepiness. RERA's, measured with an esophageal catheter, have also been associated with daytime sleepiness. Few sleep centers utilize esophageal catheters, thus many centers may not include respiratory events that are associated with <4% desaturations. In our center, we count all respiratory events and categorize them as follows: 1) apneas/hypopneas - which are assoicated with a 4% desaturation and 2) 0-3% events - which are disturbed respiratory events resulting in no desaturation or <4% desaturation and are associated with an arousal.
Methods: Our sample included every adult that underwent a diagnostic NPSG for OSA between 1/02 and 5/03 in which the AHI was less than 5/hr. (n=71). Seventeen cases were excluded due to conditions contributing to daytime sleepiness including PLMDS, narcolepsy and sedating medications resulting in n=54. There were 52% men and 48% women. The average age was 41.85 years (+/-13.39). All patients underwent NPSG's which included EEG,EOG,chin and anterior tibialis EMG, EKG, nasal/oral airflow (thermistors and nasal pressure transducers), thoracic/abdominal effort (Piezo belts) and pulse oximetry. Each patient underwent an MSLT on the day following the NPSG. Definitions: apnea - cessation of airflow for at least 10 seconds associated with at least a 4% desaturation; hypopnea - 50% reduction of airflow for at least 10 seconds associated with a 4% desaturation; 0-3% event - 50% or greater reduction in airflow, or change in respiratory effort for at least 10 seconds and associated with an arousal. The respiratory related arousals included both microarousals and arousals lasting 3 seconds or more. The AHI included only apneas and hypopneas. The Respiratory Arousal Index (RAI) included apneas, hypopneas and 0-3% events. Statistical analysis utilized t test for dependent variables.
Results: Mean TST=335.52 min.(+/-68.40); mean AHI=1.27(+/-1.17); mean RAI=24.41(+/-17.49). The disturbed respiratory events were primarily obstructive; the mean baseline arterial O2=94.24%(+/-2.10); mean O2 associated with the events =93.76%(+/-2.68); min. O2 associated with the events = 88.19%(+/-3.91). The MSLT mean SL =7.82((+/-4.52). The association between increasing RAI and increased sleepiness on the MSLT was statistically significant at p<0.000. Other significant associations with MSLT findings included TST, baseline arterial O2, average min.arterial O2, and min. arterial O2.
Conclusion: Increased RAI was associated with increased daytime sleepiness. Lower baseline arterial O2 saturation, minimum and average minimum arterial O2 saturations were also associated with increased daytime sleepiness. RAI is not the only factor responsible for daytime sleepiness in this sample. We need heightened awareness that sleep disordered breathing with minimal desaturations can be associated with sleepiness. A uniform method of identifying disturbed respiratory events needs to be developed.

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Race, Gender, Age, And BMI Differences In The Patient Population Of An Accredited University Sleep Center

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Introduction: It is well known in the history of Medicine and in medical disorders the presence of demographical differences. Reasons for these differences are multifactorial and understanding these differences is very important because they aid in health policymaking and patient education. We were interested in assessing/understanding the demographical features and differences in the area of race, gender, age and BMI of our sleep center patients.
Methods: Retrospective data review of patients seen during the year 2000-2001, who were more than 16 years of age, was done. These patients had either Baseline PSG or CPAP/BiPAP titration. Data of 136 patients were analyzed (Male=72, Female=64 & W=87, AA=48). Age: W= 49.64 ±13.18, AA=44.31 ±13.54. BMI: W=34.54 ±10.38, AA=41.02 ± 9.43. Appropriate statistical analysis was conducted using SPSS package. Descriptive measures were based on means ±s.d. Comparisons between groups were made using Student's unpaired t-test. Differences were considered significant when p<.05.
Results: Male and Female AA presented at an earlier age than whites to the center (44.31±13.54 vs. 49.64±13.18; p<.03). Male & Female AA had higher BMI than whites (41.02±9.44 vs. 34.54 ±10.34; p<.0001). AA males had higher BMI than white males (41.23 ± 9.81 vs. 34.38 ± 10.38; p<.028). No significant age difference was noted between the races in males. AA females had higher BMI than white females (40.92 ± 9.43 vs. 34.84 ± 10.56; p<.019). There was no significant age difference noted between the races in females. 80.6% of white males compared to 19.4 % of AA presented to the sleep center, a significant differ-

ence (p<.0001)
Conclusion: In summary, both male & female AA tended to present to the sleep center at a significantly early age and also have higher BMI. Another important gender difference is that AA males are significantly less represented in the sleep center suggesting that they may not be recognizing and seeking treatment. Further studies are necessary to confirm this is a geographic southern findings are consistent throughout the nation.

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Impact of a Protocol to Prioritize Patients With Severely Abnormal Overnight Oximetries for Expedited Sleep Center Evaluation

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Introduction: Many sleep disorders laboratories have prolonged wait times for polysomnography. This can result in frustrating and potentially dangerous delays for patients. We hypothesized that patients with markedly abnormal screening overnight oximetries were experiencing untoward delays in evaluation at our institution in the context of our center's long wait list, and that initiation of a program to prioritize these patients would significantly decrease delays in their sleep evaluation.
Methods: Severely abnormal ambulatory overnight oximetry was defined as an oxygen desaturation index (# of desaturation events > 4% divided by the valid recording time) AND a cumulative time with an oxyhemoglobin saturation < 90% > 15% AND a minimum saturation of < 75%. We retrospectively reviewed consecutive patients with severely oximetry criteria over a 6-month period. Calculating that an average of 1 patient a day met these criteria, we reserved one urgent consult slot a day for such patients and then prospectively assessed the effect on consecutive patients over the ensuing 6 months.
Results: Ninety-five patients (mean age 59.8 years; mean BMI 38.3 kg/m2; 27 women) which represented 3.7% of all outpatient oximetries performed met urgent oximetry criteria in the 6 months before initiation of the expedited program. Fifty-eight (61%) patients completed their sleep evaluation at our institution taking an average of 27.5 days. After initiating the program to expedite patients with severely abnormal overnight oximetries, 102 patients (mean age 62.4 years; mean BMI 38.6 kg/m2; 36 women) which represented 3.3% of all outpatient oximetries met criteria. Seventy-four (72%) patients completed their sleep evaluation at our institution taking an average of 8.6 days ($p < 0.05$ versus the pre-program group).
Conclusion: A program to target patients with severely abnormal overnight oximetries can significantly decrease delays in the sleep evaluation.

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Clinical Results With A Lab-Molded Oral Appliance In 257 Sleep Apneic Patients

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Introduction: CPAP is the gold standard treatment for obstructive sleep apnea (OSA). In spite of significant improvements in machines and masks, many patients find it very uncomfortable. Most studies indicate 20-50% discontinue use. Oral appliances have been used as an alternative. These generally have to be made by a dentist. When an oral appliance was developed that could be fashioned and titrated in one night in a sleep laboratory, a different treatment strategy became available. This study reports on 3-years of experience with such an oral appliance, on the success and failure in achieving clinically relevant results. An RDI of 5 is traditionally considered to be the level of clinical significance. Many clinicians accept a level of 10 as being satisfactory. This study, therefore, accepted an RDI of less than 5 as being a success and an RDI of 5 - 9 as a partial success.
Methods: A study of the titration results achieved in a consecutively treated group of sleep apnea patients with a customizable oral appliance in a free-standing sleep laboratory over a 3-year period. Subjects were chosen according to a prescribed protocol (RDI < 30, mean SaO2 > 92%, below 90% saturation for < 2% of time, no TMJ, no marked gag reflex, adequate teeth, and patient agreement). Patients were selected after a polysomnogram study. Clinical relevance was assessed as an RDI < 5 and partial success as an RDI < 10. The mandibular advancement device utilized in this study was the Custom Silencer (Integrated Health Technologies). The OA was molded for the patients according to the manufacturer's instructions and to the experience gained over time. The patients were then permitted a 4-week period to habituate to the use of the device while sleeping. Following this an OA titration study was performed.
Results: Two hundred and fifty seven patients met the selection criteria. The vast majority (82%) achieved a partial clinical success (RDI < 10) and a smaller majority (56%) achieved complete success (RDI < 5).
Conclusion: These results indicate a large role for oral appliance therapy in managing the typical patient seen in a general sleep laboratory population, who is an obese patient with mild to moderate sleep apnea. The ease of use of this OA and the ability to titrate it in the laboratory on one night brings clear advantages. Staff members are easily trained to mould the device to the patient's teeth. CPAP does, in common experience, produce a better resolution of the RDI and a better oxygen saturation improvement. However, a good result is often sufficient, and the convenience of use and lower cost are critical factors in acceptance and possibly compliance. There are significant saving advantages to health payers.

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Effects Of DOI (5-HT2A/2C Agonist) And 8-OHDPAT (5-HT1A Agonist) After Systemic Injections On Genioglossus Muscular Tone On Unanaesthetized Rat

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Introduction: The obstructive sleep apnea syndrome is partly due to genioglossus (GG) muscular hypotonia. The motoneurons of the XII nucleus (XIIm) which innervate the GG, are mainly controlled by direct and indirect serotoninergic pathways. The objective was to test by chronical systemic injections, a 5-HT2A/2C agonist (DOI) and a 5-HT1A agonist (8-OHDPAT) on the GG tone.
Methods: Electroencephalography, neck electromyography and GG electromyography were continuously recorded on 12 Sprague-Dawley rats. After the surgical procedure, each rat was conditioned for one week (12h/12h inverse dark-light cycle, food ad libitum). The second week rats were injected (intra-peritoneal route) at 9.00 AM and 6.00 PM with sodium chloride solution for the first 2 days (control period), with DOI (n=6, 1mg.kg-1) or 8-OHDPAT (n=6,1 mg.kg-1) for the next 2 days and a 2 days final period without injection. Each rat was its own control.
Results: No significant changes of the GG muscular tone were reported with the DOI and 8-OHDPAT during awake or sleep states. The total sleep duration was significantly decreased with the DOI and the 8-OHDPAT.
Conclusion: Our results are in contrast with previous studies which report systemic injections of the DOI and 8-OHDPAT increased the tonic and inspiratory phasic activity of the XII nerve on anaesthetized rat. Microdialysis injections into the XII nucleus of a 5-HT2A antagonist or

8-OHDPAT decreased the inspiratory phasic activity of the XII nerve on anaesthetized rat. Our experiments were done on free behaviour rats without any anaesthetic. In order to investigate therapeutic drogues and their pharmacological effects on the GG tone during sleep, route of administration and anaesthetized state must be taking into account. The direct (5 HT2A/2C) and indirect (5 HT1A) serotoninergic pathways on the XII nucleus motoneurons are probably not the main pathway to increase the GG tone on free behaviour rat after intra-peritoneal injections.

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CSF Histamine And Noradrenaline Contents In Narcolepsy And Other Sleep Disorders

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Introduction: Recent studies in animals and humans demonstrated that histamine contents are decreased in the brain (in hypocretin receptor 2 mutated Dobermans) and in the CSF (in human) of narcoleptic subjects (1,2). Considering the fact that histamine is one of the wake-promoting amines and that hypocretins excite histaminergic neurotransmission, impaired histaminergic neurotransmission may be an important pathophysiological mechanism in narcolepsy. In the current study, we measured CSF histamine content in narcoleptic subjects with and without hypocretin-deficiency, idiopathic hypersomnia (IHS), obstructive sleep apnea syndrome (OSAS) and also in the controls to examine whether histaminergic neurotransmissions are altered in narcolepsy and other excessive daytime sleep disorders. We also measured noradrenalin contents in these CSF samples for the comparison.
Methods: Fourty-two narcolepsy, 14 IHS, 18 OSAS and 66 neurological control subjects were included. Narcoleptic subjects include those with and without cataplexy. Twenty-three narcoleptics were shown to have very low CSF hypocretin levels (mean /-SEM: 43 /-1.8pg/ml), while hypocretin levels in 15 narcoleptics (242 /-11pg/ml) were in the same range of the normal controls (289 /-11pg/ml), and were thus defined as non-deficient narcolepsy. CSF samples collected between 9:00 am to 5:00 p.m., were kept and frozen (-80C) immediately until the measurements were done. The hypocretin levels of other sleep disorders (IHS: 240 /-14, OSAS: 265 /-26) were the same as those with neurological controls (289 /-11). Histamine and noradrenaline measurements were done with a fluorometric HPLC. All measurements were done blindly, with each CSF sample being measured twice, and the mean values of the two measurements being reported. For statistical analysis, ANOVA with Donferroni/Dunn were used. The statistical significance was set to <0.003.
Results: We found significantly lower histamine levels in narcoleptic subjects with hypocretin-deficient (197 /-40pg/ml, p=0.0001), without hypocretin-deficient (193 /-57pg/ml, p=0.002) and IHS (144 /-35pg/ml, p=0.0002) compared to neurological controls (409 /-31pg/ml). Noradrenaline levels were low in the patients with narcolepsy with hypocretin-deficiency (766 /-148pg/ml), narcolepsy without hypocretin-deficiency (852 /-162pg/ml) and HIS (955 /-194pg/ml), compared to controls (1399 /-109pg/ml), but only narcolepsy with hypocretin-deficient reached to a significant level (p=0.002). Histamine and noradrenalin levels in patients with OSAS (382 /-59pg/ml and 1299 /-226pg/ml) were in the same range of the controls. CSF histamine and noradrenaline values were not significantly correlated with hypocretin levels, gender and age.
Conclusion: Similar to findings reported by Nishino et al., histamine neurotransmission is decreased in hypocretin deficient narcoleptic subjects. Although Nishino et al., also reported that that reduced histamine levels were observed in a subset of hypocretin non-deficient narcoleptic subjects, our study revealed that the reduced histamine levels in the patients with narcolepsy without hypocretin-deficient and HIS, were as significant as hypocretin-deficient narcolepsy. The results that altered histamine neurotransmission is generally observed in primary EDS disorders, but not in secondary EDS (i.e., OSAS), suggesting the importance of histaminergic system for maintaining wakefulness during daytime and the pathophysiology of EDS disorders. It is critical to know whether altered histaminergic neurotransmission occurs independently from the hypocretin signaling or altered hypocretin signaling due to dysfunctions of hypocretin receptor and/or effector systems which may also be responsible for hypocretin non-deficient EDS conditions. Further studies are warranted. References: (1) Nishino S et al., Neurosci Lett 2001, 313 (3): 125-8. (2) Nishino S et al., SLEEP 2002, 25(Suppl), A476

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Incrasing Delay In Diagnosis Of Narcolepsy Is Associated With Increasing Incidence Of Sleep Paralysis In A Cohort Of Patients With Narcolepsy

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Introduction: Sleep paralysis (SP) represents an important and serious morbid event in patients with Narcolepsy: Episodes can vary in duration from one to several minutes and are usually extremely distressing especially when accompanied by hallucination. Its prevalence in the literature is between 30-62%. Our hypothesis was that a delay in diagnosis of narcolepsy in the Norwegian cohort could be associated with an increasing incidence of sleep paralysis.
Methods: The eligible population under study was selected from the Norwegian register for sleep disorders. Our cohort represent 180 pasients. A questionnaire was send to all patients. The response rate was 78%. This was supplemented by a telephone interview to all of them by one of the investigators (ES). The delay in diagnosis of narcolepsy was estimated as the difference between age of diagnosis minus the age of symptoms. This was considered as exposition, and the incidence of sleep paralysis was the outcome. Other variables were considered to be potential confounders or effect modifiers of this association. Stratification analysis and multivariate analysis were performed to adjust for multi confounders. We categorized the exposition variable in quartiles.
Results: The prevalence of sleep paralysis in our cohort was around 60%. The mean delay of diagnosis was of 15.1 years with an SD=12.5. Univariate analysis showed that patients with a delay >11 years had a risk of sleep paralysis 3.2 times higher than for a delay <=11 years with 95% CL (1.4-7.7) 2p=0.01. A stratification analysis using Mantel-Haenszel method showed that gender, higher education and living in big towns were confounders of the association delay in diagnosis as exposition and the outcome sleep paralysis. A multivariate analysis using the logistic model was used to control for multiconfounders, pinpointed that the adjusted increasing risk for a diagnostic delay >11 years as compared <=11 years on the occurence of sleep paralysis was 3.5 when adjusting for confounding effect of higher education and gender.
Conclusion: Delay in diagnosis of narcolepsy is an independent predictor of increasing frequency of sleep paralysis. Possibility of preventive action will be to lower this delay time as to reduce the occurence of sleep paralysis in patients with narcolepsy.

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Range of Effectiveness of Chronic Employment of Methamphetamine in a Father and Two Sons with Narcolepsy

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Introduction: Methamphetamine is a powerful alerting compound with a history of effectiveness in narcolepsy. However, substance abuse potential and illicit trade with impure forms has diminished the enthusiasm for its use even in otherwise refractory narcolepsy patients. From our database of patients treated with psychostimulants for narcolepsy (defined by HLA markers & polysomnography) with objective evidence of impaired attention, a family of three males treated with methamphetamine was encountered. Prior trials with alternate psychostimulants historically were ineffective. We evaluated the effect of methamphetamine therapy on daytime non-alertness, nighttime sleep as well as cognition/affect.
Methods: Retrospective analysis from a patient database of subjects treated with psychostimulants of a single family aggregate historically treated with methamphetamine for 10, 15 & 12 years respectively on our initial assessment in 1995. Review included serologic tests, nighttime sleep (sleep log), objective neuropsychological tests of attention (off & on treatment drug): Test of Variables of Attention (TOVA), Conner's Continuous Performance Test (CPT), Wisconsin Card Sorting Test (WCST) and Letter Cancellation Test (LCT), as well as daytime alertness by pupillometry and personality by Minnesota Multiphasic Personality Inventory (MMPI).
Results: Father: current age 82, dose 0.5 mg/kg, MMPI mild depression; Son 1: current age 45, dose 0.6 mg/kg, MMPI mild anxiety; Son 2: current age 41, dose 0.5 mg/kg, MMPI mild obsessiveness. All three: normalized attention on all cognitive measures, no serologic abnormality, pupillometric alertness, no decline in affect in 8 years. Only father disturbed sleep architecture, converted to modafinil 400 mg/d 5 years after our initial evaluation.
Conclusion: In this Minnesota family of three men, a father and two sons, chronic exposure to moderate dose methamphetamine demonstrated safety and efficacy for alertness, general health, psychiatric comorbidity and maintenance of cognitive function. The older patient was successfully converted to modafinil to improve sleep architecture. The frequency and characteristics of subjects for whom methamphetamine therapy is appropriate warrants further study.

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CSF Hypocretin-1 (Orexin-A) Measurement in Pediatric and Teenager Patients with Hypersomnia and/or Cataplexy

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Introduction: Narcolepsy and other sleep disorders are under-recognized in children and the final diagnosis and initiation of treatment is often delayed. This is partially due to the fact that the expression of the sleep-related symptoms in children is often different from those in adults. Hypersomnia is often expressed as a behavioral hyperactivity and/or deficient attention in children. Furthermore, polysomnographical examinations are generally difficult to perform in children, and the interpretation of the results is often difficult (especially for diagnostic purposes). An establishment of a specific diagnostic tool for sleep disorders in children would thus be an urgent issue. Recent CSF hypocretin-1 measurements and postmortem studies in narcolepsy suggest that hypocretin deficiency is the major pathophysiology of the disease. CSF hypocretin-1 in various neurologic and sleep disorders in adults further demonstrated that low CSF hypocretin-1 levels are highly specific to narcolepsy, and the CSF hypocretin measures are now being established as a new diagnostic tool. In this study, we describe the spectrum of the hypocretin deficiency syndrome by analysis of CSF hypocretin-1 levels, and clinical, polysomnographic, and HLA data in 40 pediatric and teeager patients with various sleep disorders. This is the first study to offer definitive information on the use of CSF hypocretin-1 measurement for the diagnosis of pediatric hypersomnia and/or cataplexy.
Methods: CSF samples from 40 subjects under 20 years of age with various sleep disorders were provided from 4 hospitals in Japan. Sleep disorders were diagnosed clinically and using sleep studies. Patients were classified based on their primary ICSD diagnosis, blind of HLA and hypocretin-1 results. Hypocretin-1 was measured in the unextracted CSF samples using commercially available radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA), as previously reported.
Results: Diagnosis included narcolepsy-cataplexy (n=13), narcolepsy without cataplexy (n=7), idiopathic hypersomnia (n=7), recurrent hypersomnia (n=4), cataplectic attack (n=2) and secondary hypocretin deficient hypersomnia. (n=7). The two patients with cataplectic attacks were also diagnosed as Niemann-Pick type C. Further analysis was done among narcolepsy-cataplexy, narcolepsy without cataplexy and idiopathic hypersomnia. Twelve out of thirteen patients with narcolepsy-cataplexy had HLA DR2 and low hypocretin levels. Five out of seven patients with narcolepsy without cataplexy had HLA DR2 and two of them had low hypocretin levels. Three out of six patients with idiopathic hypersomnia had HLA DR2 but none of them had low hypocretin levels. The mean age of the patients with narcolepsy-cataplexy (mean+/-SD: 9.5+/-3.2) was significantly younger than those of narcolepsy without cataplexy (15.4+/-3.1) and idiopathic hypersomnia (15.8+/-2.1). The levels of hypocretin were significantly lower in narcolepsy-cataplexy (59+/-58pg/ml) compared to narcolepsy without cataplexy (196+/-112) and idiopathic hypersomnia (231+/-42). The appearances of SOREMPs in MSLT were significantly lower in idiopathic hypersomnia (3+/-8%) compared to narcolepsy-cataplexy (81+/-27%) and narcolepsy without cataplexy (66+/-26%).
Conclusion: As same as adults, abnormally low hypocretin-1 levels are specific for narcolepsy-cataplexy in children and teenagers. The biological markers of hypersomnia and/or cataplexy, such as HLA, MSLT and hypocretin, were also same as those of adults. A measurement of hypocretin-1 level is useful diagnostic tool in pediatric narcolepsy especially when other diagnostic information (MSLT, polysomnography) is not sufficient.

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Response of Narcolepsy-Cataplexy To Treatment With Sodium Oxybate

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Introduction: There is insufficient information about the predictors of response of narcolepsy-cataplexy to treatment with sodium oxybate, and about the side effects that are commonly encountered in clinical practice. We address these issues by reviewing the outcome of patients at our institution who have been treated with this medication.
Methods: After obtaining approval from the Institutional Review Board, a chart review was conducted of all patients with narcolepsy-cataplexy who had been treated with sodium oxybate. Cataplexy was rated post-hoc on a three point scale as +++ if it was associated with falls to the floor/injuries, ++ if the muscle atonia could be countered by the patient

by holding on an object for support, and + if the muscle atonia was inconsequential, thus not requiring external support.
Results: Over a one year period, 17 patients were prescribed sodium oxybate, but 1/17 did not initiate drug therapy owing to expense considerations. The mean age of the remaining 16 subjects was 36.9 years (range 9.5-78). The mean duration of narcolepsy-cataplexy was 14.6 years (range 0.5-53). They had been treated previously with an average of 3.6 medications (range 0-8). The mean duration of treatment with sodium oxybate was 5.1 months (range 1-12), and the mean nightly dose was 5.5 grams (range 3-8; median =6 grams). Nine of the 16 (56.5%) reported improvement in cataplexy by one or more clinical grade, and 8/16 (50%) reported improved daytime alertness. A refreshed feeling upon awakening in the morning was indicated by 8/16 (50%) subjects. Of the 8 patients who expereinced no improvement on sodium oxybate, 3/8 had associated obstructive sleep apnea, 1/8 had obstructive sleep apnea plus exacerbation of cataplexy, 3/8 had prior depression or anxiety, and 1/8 developed "jitteriness." One of the depressed subjects committed a suicidal gesture. Three of these 8 have stopped using the drug. Tolerable side effects were seen in 9/16 subjects (56.5%), and have consisted of difficulty staying asleep between doses or early in the morning in 5/9, and constipation in 4/9 subjects.
Conclusion: Sodium oxybate was modestly effective in treating narcolepsy-cataplexy. A refreshed feeling upon awakening in the morning, reduction in cataplexy episodes, and improved daytime alertness were seen in about half of the subjects. Constipation and insomnia were the most common side effects. Obstructive sleep apnea, depression, and anxiety were observed in non-responders. This information might help select patients who are most likely to benefit from treatment with sodium oxybate.

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An Infant Case Of Hypersomnia With Acute Disseminated Encephalomyelitis Due To Hypothalamic Dysfunction

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Introduction: Cerebrospinal fluid (CSF) hypocretin is reported to be markedly decreased in narcolepsy/cataplexy patients. Symptomatic narcolepy is caused by hypothalamic lesion such as strokes and tumors with decreased CSF hypocretin-1 levels. However, hypersomnia without any other narcolepsy-related symptoms due to hypothalamic lesion has not been well documented. The aim of the study was to examine the CSF hypocretin-1 in hypersomnia due to hypothalamic lesion.
Methods: The patient presented hypersomnia secondary to hypothalamic lesion were employed in the study. Clinical symptoms, brain MRI, and CSF hypocretin-1 level were correlated.
Results: Case report. An 11-month-old girl was admitted to a local hospital for her somnolence. The patient was born normally, but with mild mental delay. The patient's history of illness was noncontributory. In the family history, her brother also had mild mental retardation. Since cranial computed tomography (CT) revealed multiple low-density areas mainly in the white matter, the patient was admitted to our hospital. On the physical examinations of the patient, we found minor anomalies, which were ocular telecanthus, low set ear and flat nasal bridge. On the neurological examinations, there were increased patellar tendon reflexes, and hypersomnia were observed. On electroencephalogram (EEG), mild slow waves were continued in the background activity. Brain magnetic resonance imaging (MRI) showed multiple T1-low and T2-high intensity lesions in the white matter, brainstem, bilateral hypothalamus and so on. Single photon emission computed tomography (Tc99m-PAO SPECT) revealed decreased cerebral blood flow agrees with the lesions of MRI. In the CSF, interleukin-6 (IL-6: 3.2 pg/ml) and myelin basic protein (MBP: 337.2 pg/ml) were increased, but hypocretin-1 level was undetectable (<40 pg/ml, age matched controls: 274 /-69 pg/ml). She had the diagnosis of acute disseminated encephalomyelitis (ADEM). Hypersomnia improved within three days with administration of intravenous steroids. MRI lesions and SPECT findings were gradually improved, and IL-6, MBP level in the CSF recovered to normal. However, the hypocretin-1 level increased to 60 pg/ml.
Conclusion: Decreased CSF hypocretin-1 level in the cases may reflect degree of hypothalamic dysfunction, and it can explain the mechanism of hypersomnia.

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Modafinil Improves Steer Clear Performance in Narcolepsy

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Introduction: Narcolepsy is associated with impaired performance and lapses of attention. These are likely to be consequences of excessive sleepiness. Modafinil's efficacy and safety for treating excessive sleepiness related to narcolepsy were demonstrated in more than 500 patients during two 9-week, multicenter, randomized, double-blind, placebo-controlled trials. Modafinil administered daily (200 mg or 400 mg) significantly improved wakefulness, measured both objectively and subjectively. During these trials, modafinil was compared with placebo using a performance task requiring sustained attention.
Methods: Patients diagnosed with narcolepsy according to International Classification of Sleep Disorders criteria were enrolled. Inclusion criteria required objective Multiple Sleep Latency Test evidence of excessive sleepiness (mean sleep onset latency of <8 minutes) and 2 or more naps with REM sleep. The Steer Clear task assesses an individual's ability to avoid hitting obstacles during a 30-minute driving-like sustained attention test. Steer Clear was performed at baseline and weeks 3, 6, and 9 during double-blind treatment. In one of the two multicenter trials, patients were also assessed at week 1.
Results: Modafinil significantly improved performance (measured as change from baseline compared to placebo at weeks 3, 6, and 9). The mean (±SD) percentage of obstacles hit at baseline (n=522) was 7.8 (±9.8) for placebo, 8.2 (10.7) for modafinil 200 mg, and 7.0 (8.2) for modafinil 400 mg. No significant differences were found between placebo and modafinil at week 1; the mean percentage of obstacles hit was 9.3 (10.1) for placebo, 6.4 (10.6) for modafinil 200 mg, and 6.7 (10.3) for modafinil 400 mg. At week 3 (n=516), the mean percentage of obstacles hit was 8.2 (11.0) for placebo, 6.2 (9.7) for modafinil 200 mg (p=.002 vs. placebo), and 4.9 (9.4) for modafinil 400 mg (p=.001 vs. placebo). At week 6 (n=504), the mean percentage of obstacles hit was 7.9 (12.3) for placebo, 5.7 (9.8) for modafinil 200 mg (p=.004 vs. placebo), and 5.4 (8.8) for modafinil 400 mg (p=.05 vs. placebo). At week 9 (n=503), the mean percentage of obstacles hit was 8.7 (12.3) for placebo, 5.9 (10.5) for modafinil 200 mg (p=.004 vs. placebo), and 5.2 (10.6) for modafinil 400 mg (p=.004 vs. placebo).
Conclusion: Modafinil treatment significantly improves performance on a task requiring sustained attention in patients with narcolepsy. These results are consistent with results of similar trials in other patient populations.

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Expression Of A Poly-Glutamine-Ataxin-3 Transgene In Orexin Neurons Induces Narcolepsy-Cataplexy In The Rat

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Introduction: Human narcolepsy is likely to be caused by a degeneration of orexin- (hypocretin-) expressing neurons in the lateral hypothalamus (LH). Mice in which the neurotoxic poly-glutamine-ataxin-3 fragment is expressed under control of the human prepro-orexin promoter (orexin/ataxin-3 transgenic mice) selectively and completely lose orexin neurons during adolescence, resulting in unequivocal expression of narcolepsy (Hara et al., 2001 Neuron 30:345). Because the rat is a species widely used in sleep research, and because more sophisticated physiologic methodologies are currently available for the rat, we generated orexin/ataxin-3 transgenic rats. Here we report the histological and vigilance state characterization of orexin/ataxin-3 transgenic rats in detail.
Methods: Orexin/ataxin-3 transgenic rats (Sprague-Dawley) were created using the transgenic construct described previously (Hara et al., 2001 Neuron 30:345). Rats were housed under a 12:12 L:D cycle and standard sleep recording conditions. In one selected line, brains of male transgenic and wildtype littermates (at 4, 7, 10, 13, and 17 weeks) were examined for immunoreactivities of orexin, melanin-concentrating hormone (MCH), and Myc tag on the transgene product. Using a minimally restraining screwless ultra-light weight implant system, we recorded EEG/EMG signals in male hemizygous transgenic (N=8) and male wildtype (N=20) rats at 17 weeks of age, characterized their vigilance states, and performed power spectral analysis on selected artifact-free representative epochs. We also monitored the behavior of the animals by infrared video photography during the dark period while recording EEG/EMG.
Results: The orexin/ataxin-3 transgene immunoreactivity (Myc tag) colocalized exclusively within orexin neurons in the LH; no ectopic expression was found. Orexin-immunorectivity continuously degraded over time, until at 17 weeks of age the transgenic rats exhibited virtually total postnatal loss of orexin-positive neurons in the LH, and orexin-containing projections were essentially undetectable. Genotypes showed no differences in regard to MCH immunoreactivity. Loss of orexin in orexin/ataxin-3 hemizygous rats resulted in a narcoleptic phenotype, with decreased latency to rapid eye movement (REM) sleep (4.5 ± 0.2 min. vs. 5.8 ± 0.3 min., $p<0.01$, hemizygous vs. wildtype, respectively) and a reversal of REM sleep distributions between photoperiods. Wakefulness time was reduced during the dark phase (460 ± 19 min. vs. 516 ± 10 min., $p<0.05$), with a marked fragmentation of vigilance states. Direct transitions from wakefulness to REM sleep, a defining characteristic of narcolepsy, occurred frequently. Brief episodes of muscle atonia and postural collapse, resembling cataplexy, while rats maintained the EEG characteristics of wakefulness (as judged by power spectral analysis), were also noted.
Conclusion: Transgenic expression of a neurotoxic ataxin-3 polypeptide in rats selectively and completely eliminated orexin neuropeptide expression in the LH. This led to a phenotype that closely resembled narcolepsy. Orexin/ataxin-3 transgenic rats should therefore be a valuable addition to the existing canine and murine models of the disorder.

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The Association Between Narcolepsy and REM Sleep Behaviour Disorder (RBD)

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Introduction: REM sleep Behaviour Disorder (RBD) is a form of motor dyscontrol due to loss of REM related muscle atonia and is characterised by complex, vigorous and frequently violent dream enacting behaviour during REM sleep. RBD is usually idiopathic or secondary to neurological problems such as Parkinsons disease. This study looked at the association of RBD with another sleep disorder, narcolepsy.
Methods: 78 questionnaires were sent to known narcoleptics chosen at random from those with contact details available at the centre. Positive questionnaire results were followed up with a telephone interview. Limited polysomnography (PSG) data was also analysed
Results: 55 patients responded (response rate 71%). Of these, 20 (36%) had RBD. The typical RBD patient is an older male (mean age of onset 60.9yrs, 87% male), however in this study, females were as likely to have RBD as males, and the mean age was 41 yrs. 68% of patients that regularly experienced cataplexy and the associated symptoms of narcolepsy (sleep paralysis, hypnogogic halucinations and automatic behavior) had RBD, compared to 14% of those that never or rarely experienced these symptoms.
Conclusion: This study shows a stronger relationship between these disorders than the previously published figure of 7-12%, (Schenck and Mahowald, 1992). This is significant clinically as RBD is a potentially distressing but readily treatable disorder. It follows that narcoleptics, especially those with cataplexy and other associated symptoms, should be questioned about symptoms of RBD and treated accordingly. Similarly, anyone presenting with RBD should be investigated for symptoms of narcolepsy, particularly if they are female, or of a younger age group than would otherwise be expected.

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Time Course Of Survival Of Hypocretin Neuronal Transplants Into The Pons Of Adult Rats

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Introduction: The sleep disorder narcolepsy is now considered a neurodegenerative disease since there is a massive loss of neurons containing the neuropeptide, hypocretin (HCRT), and narcoleptic patients have very low CSF levels of HCRT. Because neuronal transplants and gene transfer have been successfully applied to ameliorate Parkinson's disease symptoms we have begun to investigate whether such methods could also be applied to HCRT neurons. Currently, there is no data that transplants of the HCRT neurons can survive when grafted into host tissue. Here we examined the time course of survival of HCRT-containing neurons transplanted into the pontine reticular formation, a region traditionally regarded to be key for REM sleep generation. Despite this, we have found that the loss of HCRT input is critical to sustain normal levels of alertness during the active period in the pontine reticular formation.
Methods: A suspension of cells from the lateral hypothalamus (LH) of 4-8 day old rat pups was injected into the pons (midline, at the level of

the locus coeruleus) of adult rats. Control rats received cells from the cerebellum, tissue that is devoid of HCRT neurons. The cell suspension was mixed in the following media: DMEM, supplemented with 4.5µg insulin (Sigma), 100 U/ml penicillin, 100 mg/ml streptomycin and 2.5 mg/ml fungizone. A single bolus (5µl) of cells was placed in the pons. The adult rats were sacrificed one to 36 days after transplant, and cryostat-cut coronal sections of the brainstem were examined for presence of HCRT neurons.

Results: Clearly defined and intact HCRT containing somata and varicosities were clearly visible in pons of rats sacrificed 24h after transplant of LH cells, but not in rats receiving cerebellar tissue. Six to nine days post-transplant the number of HCRT-labeled neurons was about half that seen on the day 1, and by day 36 we estimate that only about 5% of HCRT neurons survived. The surviving neurons had integrated into the host brain as evidenced by clearly defined processes. In the graft area a dense collection of HCRT-immunoreactive fibers and varicosities were evident. We are staining the remaining tissue for presence of other peptides, such as melanin concentrating hormone (MCH) that is also present in the LH to determine survival of other LH neurons.

Conclusion: Currently, there is no data that HCRT neurons can be transplanted. Our findings demonstrate that HCRT neurons can survive in a brain region implicated in sleep control and where such neurons are not normally present. Further studies are needed to assess the potential utility of LH transplants to ameliorate narcoleptic symptoms.

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Mood, Perceived Stigma and Health Status Self-Disclosure of Young Adults with Narcolepsy

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Introduction: Middle-aged and older adults with narcolepsy report experiencing deleterious effects on their personality and social relations because of this disorder. However, little systematic information is available about how narcolepsy affects the mood and social relations of younger people with this disorder. The purpose of this presentation is to describe the mood and social relations of young adults with narcolepsy (YAWN) 18-35 years of age compared to healthy controls in the same age group. The sample consists of 123 YAWN who reported meeting the ICSD narcolepsy diagnostic criteria (M 28, F 95, mean age = 27.1+/-4.7) and were solicited for voluntary participation from a CNR mailing list, and 94 young adult healthy controls without any clinical evidence of a sleep disorder (34 M, 60 F, Mean age = 25.6+/-3.9).

Methods: Participants completed a mailed, nine section, previously validated Young Adults Health Questionnaire (YAHQ) consisting of investigator-designed and standardized instruments. Control participants were acquaintances of the YAWN respondents, and volunteers solicited through UIC campus advertisements. Mood was assessed with the Hospital Anxiety and Depression Scale (HADS), a 14-item measure of anxiety and depression that uses a 4-point Likert scale for respondents to rate how they felt during the past 7 days. The Stigma and Social Impact Scale (SSIS), a 30-item measure modified for use in this study, consists of four subscales and uses a 4-point Likert scale for respondents to rate how stigmatizing they felt their health condition was in social situations for the past 4 weeks. Additionally, 11 items that had been previously validated with HIV patients were used to measure attitudes about self-disclosure of their health condition.

Results: Repeated measures ANOVA revealed there were no significant mean differences between groups on the anxiety and depression subscales of the HADS (F1, 215=.004, p .95) which were below the suggested cut point of greater than 11 for both groups. YAWN compared to controls reported experiencing significantly more stigma (repeated measures F3,211 = 37.56, p .000) on the mean of all four subscales of the SSIS (independent groups t-test, corrected p .0125): social rejection, 17.8+/-5.8 versus 10.6+/-3.3; financial insecurity, 7.3+/-2.8 versus 4.1+/-1.8; internalized shame, 10.2+/-3.4 versus 6.9+/-2.8; social isolation, 17.1+/-5.3 versus 9.1+/-3.7. Three of the four SSIS mean subscale scores for YAWN approximated those reported for HIV patients. Additionally, YAWN were significantly more hesitant to disclose information about their disorder/health status to others (independent groups t-test = 8.8, p .000, 23.8+/-7.8 versus 15.7+/-5.8), a finding which is again somewhat similar to HIV patients.

Conclusion: YAWN compared to controls in their same age range reported feeling set apart and inferior to others because of their disorder symptoms, and hesitant to disclose their disorder to others because of fears about the consequences and reaction they would receive.

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Distribution Of Hypocretin (Orexin) Immunoreactivity In The Hypothalamus Of Normal And Narcoleptic Horse

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Introduction: Human narcoleptics have an 85%-95% reduction in the number of hypocretin (Hcrt) neurons and gliosis in the hypocretin cell region (Thannickal et al., 2000). Hcrt receptor -2 mutant narcoleptic Dobermans have degenerative changes in basal forebrain, septal and amygdala regions (Siegel et al., 1999) but no loss of Hcrt neurons. In this study we examined the distribution of hypocretin-immunoreactive cell bodies and fiber distribution in a normal and a narcoleptic horse.

Methods: The hypothalami of one narcoleptic and one normal horse were used. The normal horse was 6 year old thoroughbred gelding. The narcoleptic horse was 10 year old thoroughbred gelding with idiopathic hypersomnia. This horse has been suffering from episodes of sleepiness. The episodes occurred both in the stable and in the field. The incidence of attacks was as many as thirty episodes in three hours. The collapses were hard and if stimulated during the episodes the horse regains same control. Sections were cut at 40 µm and immunostained for Hypocretin-2 (Orexin B). The following hypothalamic nuclei were examined: anterior, periventricular, paraventricular, supraoptic, arcuate, dorsal, dorsomedial, ventromedial, lateral, posterior, tuberomammillary, and mammillary hypothalamus. The cell and fiber distribution, and the density of varicosities within individual axons were counted using the Neurolucida program (Microbright Corp). Analysis was performed by using the Neurolucida program.

Results: In the normal, immunoreactive cell bodies were found in the anterior, dorsal, dorsomedial, ventromedial, lateral and posterior hypothalamic nuclei. The highest density (20.58 cells/mm2) of Hcrt cells found in dorsal hypothalamic nucleus. In contrast, in the normal human, the maximum density of Hcrt cells was found in the dorsomedial hypo-

thalamic nucleus. Two distinct types of cells were identified on the basis of cell size. The cells with smaller (mean area 215 μm2 with a roundness index 0.25) generally gave rise to a single dendrite or were spindle shaped. The cells with larger (mean area 673 μm2 with a roundness index of 0.41), were generally multipolar. In the control brain, Hcrt fiber density was maximal in paraventricular nucleus (63.0 fibers/mm2) and lowest in mammillary nucleus (19.0 fibers/mm2). The average density of varicosities was 20.68/100 μm and the mean spacing was 5.5 μm. There was no significant difference in the distribution and density of Hcrt cell body, fibers and varicosities in narcoleptic horse from control.
Conclusion: We see both similarities and differences in the distribution of hypocretin cells between the normal horse, dog and human. We see no abnormality in the distribution of Hcrt cell body and fibers in the narcoleptic horse. In this respect, the narcoleptic horse appears to resemble the genetically narcoleptic dog.

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Risks of High Dose Stimulant Use for Disorders of Excessive Somnolence: A Case-Control Study

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Introduction: Occasional patients with narcolepsy or idiopathic hypersomnia are prescribed stimulants at doses exceeding published guidelines, as standard doses do not provide adequate alertness. We previously reported a case series of 58 patients, describing high frequencies of psychiatric disease, hypertension and tachyarrhythmias (Sleep 2002;25:A235). We now report a case-control study, comparing the high-dose group with a matched sample of patients taking standard doses of stimulants.
Methods: We used the Mayo Narcolepsy Research Center database to identify all patients treated for narcolepsy or idiopathic hypersomnia between 1950 and 2000 with stimulants at dosages ≥ 120% of the maximum recommended by the ASDA (Sleep 1994;17:348-351). The minimum daily dose used was 120 mg methylphenidate, 120 mg dextroamphetamine, 100 mg methamphetamine, 180 mg pemoline. We identified a control subject for each patient, matching for diagnosis, gender, age at diagnosis and duration of disease. Records were reviewed and data abstracted and analyzed. Fishers exact test and Wilcoxon rank sums test were used for statistical analyses.
Results: Fifty-eight patients and 58 controls were identified. There were no significant differences between gender, diagnoses, ages of onset and diagnosis, and duration of disease through end of the study from onset (mean high dose group 34.7 years versus 36.9 years) or diagnosis (22.6 years versus 20.3 years) . The frequency of psychosis, paranoia or disordered thinking (24% versus 5%), alcohol or polydrug abuse (24% versus 7%), and psychiatric hospitalization (22% versus 7%) was significantly higher in the high dose group. Occurrence of physician diagnosed depression was not significantly different in the 2 groups (33% versus 31%). Suicide (2% of high dose group), attempted suicide (5%), and drug seeking behavior (multiple sources or alleged lost prescriptions) (7%) occurred only in the high dose group, but did not reach statistical significance. The frequency of hypertension (43% versus 41%) and cardiovascular disease (17% versus 17%) did not differ between the groups. Significantly more high dose patients experienced tachyarrhythmias (19% versus 7%) and anorexia or weight loss (19% versus 2%).
Conclusion: This study demonstrated a significantly higher occurrence of psychosis, disordered thinking, paranoia, substance abuse and psychiatric hospitalization in patients using high dose stimulants compared to standard doses. Depression was equally prevalent in the 2 groups. Hypertension and cardiovascular disease were not more frequent in the high dose group, although supraventricular tachyrhythmias were more common. Anorexia and weight loss were more frequent compared to the controls. Our use of a case-control methodology suggests that the complications noted were directly related to the use of high dose stimulants. However, it is possible that patients predisposed to developing certain psychiatric disorders may also be predisposed to requesting or requiring higher doses of stimulants. Irrespective of which explanation is correct, our results suggest that clinicians should be very cautious in prescribing higher than recommended doses of stimulants. The presence of prior psychiatric disorders should be considered and patients should be carefully monitored for the development of psychosis, thought disorder, substance abuse, tachyrhythmias, anorexia and weight loss.

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Wake Promoting Effects of Thioperamide, a Histamine H3 Antagonist in Orexin/Ataxin-3 Narcoleptic Mice

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Introduction: Loss of hypocretin signaling causes narcolepsy in humans and animals. Recent experiments demonstrated that the histaminergic system is one of the important executive systems of the hypocretin signaling for promoting wakefulness. Furthermore, an impaired histaminergic system is suggested in human and canine narcolepsy. Although histamine or histaminergic H1 agonists are likely to promote wakefulness, systemic administration of these compounds are likely to induce various side effects mediated by peripheral H1 receptor stimulation. Histamine H3 receptors are regarded as inhibitory autoreceptors, and are enriched in the central nervous system. H3 antagonists may thus have a significant therapeutic application for excessive daytime sleepiness associated with narcolepsy. We therefore assessed the wake-promoting effects of thioperamide (a potent H3 antagonist cross blood brain barrier) in the mice narcoleptic model (i.e., orexin/ataxin-3 transgenic [TG] mice,) and the effects were compared with those in WT mice.
Methods: Male TG+/- (n = 8) and WT littermate mice (n=8) from N4 generation (C57BL6/DAB backcrossed to C57BL6 mice) were used. The mice were anesthetized and surgically prepared for EEG and EMG recording. Following 3 weeks of recovery, they were maintained in a 24-hr light-dark cycle (LD12:12) within separate compartments in a sound-attenuated stainless steel recording chamber and were acclimated to the recording apparatus for at least three days prior to the initiation of experimental observations. The mice were subjected to intraperitoneal injections of two doses (2, 4 mg/kg) of thioperamide and one vehicle (50%DMSO) injection. These 3 treatments were delivered over a three-week period, with one injection every week. Injections were made at ZT6 and followed by a 24–hr post treatment period (during which time recording chambers remained sealed). Each 10 second Epoch is classified as wake, REM sleep (REM), or non-REM sleep (NREM) by visual scoring.
Results: Thiopiramide increased in wake and reduced NREM and REM sleep in a dose dependent manner both in TG mice and WT mice.

Interestingly, wake-promoting effects of thioperamide were more prominent in TG mice especially in the initial phase (i.e., the first 3 hours). The amount of time spent awake after 2 mg/kg thioperamide was 206% of that seen after vehicle injection in TG vs. 172% in WT. The amount of time spent awake after 4 mg/kg thioperamide was 261% of that seen after vehicle injection in TG vs. 232% in WT. As previously reported by Hara et al., the mean bout length of wake (1.79±0.30 vs. 2,55±0.32 min) and NREM (4.27±0.49 vs. 5.67±0.55 min) were shorter in TG mice. The mean wake bout lengths in both genotypes became longer after thioperamide administration, while those for NREM were shorter.

Conclusion: The H3 antagonist, thiopiramide, significantly enhanced wakefulness in both hypocretin/orexin deficient narcoleptic (TG) and WT type mice. TG mice were however, more sensitive to thiopiramide, and larger wake-promoting effects by thiopiramide were observed in TG mice. As it has been suggested in human and canine narcolepsy, decreased histaminergic neurotransmission may also exist in these animals, and subsequent changes in the histaminergic receptor sensitivity (such as increased postsynaptic H1 receptor sensitivity) may account for the enhanced wake-promoting effects of thiopiramide in TG mice. H3 antagonist may thus be another therapeutic option for the management of excessive daytime sleepiness associated with impaired hypocretin neurotransmission (i.e., narcolepsy), and further studies are warranted.

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HLA DQB1*0602 Status is Related to CSF Hypocretin-1 Levels in Narcoleptic Patients without Cataplexy

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Introduction: Narcolepsy without cataplexy is diagnosed by a short MSLT mean sleep latency, the presence of at least 2 sleep onset REM periods, and exclusion of other sleep disorders such as insufficient sleep syndrome and OSA. It is uncertain whether this disorder is homogeneous or may include one subgroup related to narcolepsy with cataplexy and another related to idiopathic hypersomnia. 85-95% of narcoleptic patients with cataplexy are HLA DQB1*0602 positive, and CSF hypocretin-1 levels < 110 pg/ml are sensitive markers of the disorder. 35-56% of narcoleptic patients without cataplexy are HLA DQB1*0602 positive. The majority of this group has normal CSF Hcrt-1 levels. We hypothesized that narcolepsy patients without cataplexy positive for HLA DQB1*0602 would differ in clinical characteristics, PSG findings and CSF hypocretin-1 levels from those negative for the antigen.

Methods: We used the Mayo Narcolepsy Research Center database to identify 43 patients meeting strict diagnostic criteria for narcolepsy without cataplexy whose HLA status was known. Inclusion criteria were a history of EDS but no cataplexy, a PSG with an AHI <10, and an MSLT with mean latency <8 minutes and >1 SOREMP. HLA determinations were performed for research purposes and were not used diagnostically. CSF Hcrt-1 levels were measured in 13 patients. Clinical findings, PSG data and CSF Hcrt-1 levels were compared between the HLA positive and HLA negative groups.

Results: 16/43 patients (37%) were HLA DQB1*0602 positive and 27 HLA negative (63%). 3/4 HLA DQB1*0602 positive patients had CSF Hcrt-1 levels <110 pg/ml (93, 102 and <40 pg/ml) compared to 0/9 HLA negative patients (p=0.01, Fishers exact test). No significant differences were noted between the 2 groups with respect to: gender, age of onset of sleepiness, presence of sleep paralysis or hypnagogic hallucinations, family history of narcolepsy, history of autoimmune disease (38% in HLA + group versus 26%), mean PSG sleep efficiency (87% versus 91%), PSG REM latency (50 min versus 67 min), periodic limb movement index (15.3 versus 12.5) or mean sleep latency on MSLT (3.9 min versus 4.2 min).

Conclusion: Positivity for HLA DQB1*0602 in narcoleptics without cataplexy was associated with CSF Hcrt-1 levels <110 pg/ml. The 2 groups were not distinguishable by any other characteristics. The results suggest that the HLA positive group may be a forme fruste of narcolepsy with cataplexy, having partial Hcrt-1 deficiency sufficient to cause sleepiness but not cataplexy. As in narcolepsy with cataplexy, an autoimmune pathogenesis is possible. The HLA negative group may represent a different disorder of uncertain pathogenesis more closely related to idiopathic hypersomnia than narcolepsy with cataplexy.

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Clinical features and frequency of HLA-DQB1*0602 in Korean narcolepsy patients

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Introduction: Narcolepsy, a sleep disorder characterized by excessive daytime sleepiness, hypnogagic hallucination, sleep paralysis, abnormal rapid eye movement(REM) sleep and cataplexy has been known to be highly associated with the human leukocyte antigen(HLA) DR2 and DQB1*0602. Especially cataplexy, one of the major symptoms in narcolepsy has been to be linked with HLA-DQB1*0602. This study was designed to investigate the frequency of HLA-DQB1*0602 in the Korean narcolepsy patients and controls, and to compare clinical features and frequency of DQB1*0602 of the narcolepsy patients with or without cataplexy.

Methods: The subjects were 50 narcoleptic patients(mean age : 28.0 ± 14.1, 27 men and 23 women) who were confirmed by polysomnography and multiple sleep latency test(MSLT) as well as clinical history and symptoms at the Catholic University St. Vincent's Hospital Sleep Disorders Clinic. Patients who were co-morbid with other hypersomnic sleep disorders such as sleep apnea or periodic limb movements during sleep were excluded. All patients and 21 controls have done HLA typing for the presence of DQB1*0602. Clinical variables were examined by semi-structured interview for narcolepsy patients.

Results: 1) Average sleep latency was 2.0 ± 1.6 minutes and average frequency of SOREMPs(sleep-onset REM periods) was 3.2 ± 1.4 by MSLT in narcolepsy patients. 2) Characteristic symptoms of narcolepsy were investigated as follows: excessive daytime sleepiness(100%), cataplexy(82%), sleep paralysis(60%) and hypnagogic hallucination(60%). 3) Prevalence of involved regions when cataplexy was developed were knee and leg(97.6%) and jaw(29.3%). 4) Most triggering factors for cataplexy were laughing(85.4%) and joking(73.2%). 5) The positivity of HLA-DQB1*0602 of patients and controls were 88%, 23.8% respectively(p=0.000). 6) In cataplexy-positive narcoleptics, compared with cataplexy-negative patients,menifested decreased sleep latency(1.7 ± 1.4 minutes vs. 3.2 ± 1.9minutes)(p=0.015)and increased frequency of SOREMPs(3.5 ± 1.1 vs. 1.4 ± 1.3)(p=0.000) ,and HLA-DQB1*0602(95.1% vs. 55.6%)(p=0.001) were noted.

Conclusion: High frequency of HLA-DQB1*0602 in Korean narcolepsy patients might suggest that HLA-DQB1*0602 is likely to be a strong genetic marker in all ethnic groups and one of the most important pathogenesis. In addition, significant differences of clinical symptoms and frequency of HLA-DQB1*0602 between cataplexy-positives and cataplexy-negatives suggest that cataplexy, pathognomic symptom in narcolepsy, could be a predictable factor for the degree of symptom severity.

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Atypical Presentations And Early And Abrupt Onset Of Orexin-Deficiency Narcolepsy In An Infant With Klinefelter Syndrome

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Introduction: Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and cataplexy. The symptoms of narcolepsy may begin in childhood but the presentation may be different in children from that in adults. Recent observation of decreased orexin levels in cerebrospinal fluid (CSF) in patients with narcolepsy has made it possible to diagnose patients who have early onset or atypical symptoms. We report an orexin-deficiency narcolepsy in a 4-year-old boy with Klinefelter syndrome who have early and abrupt onset, very frequent atonic episodes, without apparent daytime sleepiness, and discuss the pathomechanism.
Methods: The 4-year-old Japanese boy was referred to our hospital because of frequent atonic episodes and psychomotor delay. At the age of 2-year-3-month he had a cold and fever for four days. On the fifth day of the illness, fever subsided but gait disturbance developed because of frequent atonic episodes of the whole body. He was admitted to other hospital. Electroencephalogram (EEG), MRI imaging showed no abnormal findings. His episodic weakness gradually improved and localized to face, neck, and trunk in subsequent ten days. His frequent atonic episodes continued, meanwhile, his family noticed that laughing, exciting, or tickling triggered his atonic episodes. He denied daytime sleepiness, and his family also did not notice his daytime sleepiness. He had delayed developmental milestones: he walked at 1 year 7 months, spoke meaningful words at 2 years 3 months, and talked phrases at 3 years. Our assessment included clinical history, multiple latency test (MSLT), EEG during the cataplectic attacks, brain MRI imaging, Tc-99m ethyl cysteinate dimer (ECD) SPECT imaging of cerebral blood flow, chromosomal analysis, human leukocyte antigen (HLA) typing, and CSF orexin level. CSF orexin level was measured using radioimmunoassay kits (Phenix Phaarmaceuticals, Belmont, CA) as previously reported.
Results: He tended to keep his mouth open, but there had no dysmorphic features. The external genitalia was normal in size and shape. Neurological examination showed slight hypotonia and decreased deep tendon reflexes. His IQ was 71 on Tanaka-Binet Test. Chromosomal analysis revealed 47; XXY. The findings of investigations including complete blood count, serum electrolytes, liver function tests, renal function tests were normal. Video-EEG showed no epileptic discharges during atonic episodes triggered by laughing and exciting. So we conclude those were cataplectic attacks. In MSLT, his sleep latency was calculated from the time that his mother held him up because he refused to lie on bed. The MSLT showed mean sleep latency of 2.8 minutes and two sleep onset REM periods during four naps. Brain MRI imaging was normal. During awake period, SPECT showed higher uptake of ECD on the right thalamus and right temporo-parieto-occipital cortices. HLA typing was positive for DRB1*1501/DQB1*0602. His CSF orexin level was below the detection limit (< 40 pg/ml).
Conclusion: The clinical history and symptoms of the patient were not typical. He had very acute and early onset of frequent cataplexy after suspected infectious episode, but had not obvious daytime sleepiness. Our examinations confirmed the diagnoses of orexin-deficiency narcolepsy and Klinefelter syndrome. There was no report on this association. We can only speculate the possibility that X-chromosome abnormality may have some role in this atypical symptoms, and unusually abrupt and very early onset of narcolepsy in this case.

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The Development Of Monoclonal Antibodies Against Hypocretin-1 (Orexin A)

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Introduction: The hypocretins (also called orexins) are two neuropeptides (hypocretin-1 and -2) synthesized in neurons whose cell bodies are located in the lateral perifornical hypothalamus. Hypocretin neurons project throughout the central nervous system and have been implicated in a variety of physiological mechanisms. Most importantly, these neurons appear to play a central role in the maintenance of wakefulness. Hypocretin-1 levels are low or undetectable in the cerebrospinal (CSF) from the majority of patients with HLA DQB1*0602 narcolepsy-cataplexy. Measurement of hypocretin-1 has therefore been proposed as a diagnostic tool in narcolepsy. To date, measurement of hypocretin-1 has been carried out using commercially available radioimmunoassays. We therefore, developed monoclonal antibodies against hypocretin-1 to standardize the specific measurement of this peptide.
Methods: Mice were immunized against hypocretin-1 using peptide conjugated to bovine serum albumin with carbodiimide. Following primary immunization with conjugate in complete Freunds adjuvant, Three booster injections of conjugate (in incomplete Freunds adjuvant) were given at 6-weekly intervals. High titer antibodies (measured by enzyme-linked immunoassay, ELISA) were observed after the second booster injection. Cross-reactivity of the polyclonal antibodies with possible related peptides including the secretin-glucagon family and the bombesin family was tested. One mouse with serum that reacted at high titer to hypocretin-1 with no cross-reactivity to other peptides was chosen. Spleen was harvested and fusion with myeloma cells carried out. Over 600 clones were obtained which were systematically tested by ELISA for binding to hypocretin-1. Of these, several clones were finally selected (8, 149, 153, 197, 226, 284, 310) which exclusively reacted with hypocretin-1. One clone (153) showed reactivity to both hypocretin peptides. Subloning was carried out by limiting dilution until monoclones were obtained. Supernatants of clones were tested by ELISA and immunocytochemistry. All clones were tested using immunocytochemistry using rat brain tissue. One clone (310) was also tested using immunocytochemistry on perfused dog and paraffin-embedded human brain tissue. Ascites was induced using the monoclones and tested in radioimmunoassay.
Results: Every subclone was IgG positive and kappa light chain positive except 8 and some subclones of 197, which were kappa light chain negative. Supernatants from all clones showed excellent reactivity to hypocretin-1 neurons and fibers by immunocytochemistry at dilutions up to 1:5000. Little non-specific background was observed. Clone 310 also showed reactivity against hypocretin neurons and fibers in dog and human brain tissues. Ascites from one clone (number 8) was used in competitive radioimmunoassay showing great sensitivity (five-fold greater sensitivity compared to currently available assays using polyclonal rabbit antibodies). Hypocretin-1 in the CSF was easily detected using only 1/4-1/5 CSF volume of reported assays.
Conclusion: The development of monoclonal antibodies will advance research into the physiology and pathophysiology of the hypocretin system. It is now possible to accurately measure and standardize the assay for hypocretin-1 in the CSF and other body fluids.

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Attenuated Novelty Seeking Behavior and Amphetamine Induced Ambulation in Orexin/Hypocretin Knockout Mice

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Introduction: The abuse of psychostimulants is a serious and growing problem in the United States. Amphetamine-like psychostimulants have been prescribed for the treatment of narcolepsy for over 60 years. Considering the prevalence of narcolepsy (1/2000) and the fact that about 95% of narcoleptic patients are currently treated with pharmacological compounds, the total cumulative number of narcoleptic patients receiving psychostimulants is large. Nevertheless, psychostimulant abuse in narcoleptic subjects is extremely rare. The major pathophysiological mechanism of human narcolepsy is now revealed to be a loss of orexin/hypocretin signaling due to orexin ligand deficiency. Orexin administration in rats induces hyperlocomotion and stereotypy and excites midbrain dopamine neurons, an important system for psychostimulant abuse. Thus, orexin deficient-narcolepsy may be resistant to psychostimulant abuse. To experimentally determine whether orexin-deficient narcolepsy is indeed resistant to psychostimulant abuse, we first examined novelty-seeking behavior in a new housing environment in prepro-orexin knockout (KO) and wild type (WT) mice. Greater locomotor reaction during exposure to a novel environment is considered to be an indication of drug abuse susceptibility. We also assessed acute effect of amphetamine on locomotion in these animals.
Methods: Male prepro-orexin KO mice (n=19; N3, C57BL/6J-129/SvEv backcrossed to C57BL/6J) and wild-type (WT) littermates (n=19) were used. Locomotor activity was assessed using a home cage monitoring system equipped with horizontal 16 infrared red lights (AccuScan Instruments, INC). On the experiment day, each mouse was placed in a test cage (same as home cage but clean setting) for 5 hrs starting at zeitgeber time (ZT) 1 (baseline). Locomotion (ambulation) was calculated from the number of consecutive beam breaks in more than two adjacent beams. Mice were then injected with amphetamine (0, 1or 5mg/kg/10ml saline) at ZT 6, and ambulation was monitored for another 2hrs. Each animal was drug naive and received only one injection.
Results: In the baseline phase, KO mice showed significant lesser ambulation (6937±423, mean±S.E.M) than WT (9690±529) overall (p=0.001). This difference was prominent in the initial hours, and those in 1-4 hours reached to statistical significant levels. These results suggest that novelty-seeking activity is attenuated in orexin ligand deficient mice. The injection of saline at ZT 6 did not induce significant differences in ambulation between KO and WT mice. Amphetamine did enhance ambulation in both KO and WT mice in a dose-dependent manner. However, this effect was significantly attenuated in KO mice for each drug dose during both the first 1hr (KO vs. WT; 1mg/kg: 1044±223 vs. 2365±469, 5mg/kg: 2945±448 vs. 3947±516) and 2 hr periods (1mg/kg: 1388±327 vs. 2758±463, 5mg/kg: 5113±586 vs. 7257±955) recorded.
Conclusion: Our results demonstrated that novelty-seeking in a new housing environment is significantly attenuated in KO mice compared to WT mice. Moreover, the acute effect of amphetamine (increased ambulation) in KO mice is significantly attenuated. These results may indicate the resistance of the psychostimulant abuse in KO mice. Further investigation of amphetamine reward responses (behavioral sensitization, conditioned place preference test) in orexin/hypocretin-deficient mice is warranted.

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Cerebral Glucose Metabolism in Patients with Narcolepsy

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Introduction: Narcolepsy is characterized by excessive daytime sleepiness and cataplexy. Recently, the gray matter reduction of hypothalamus was revealed by SPM analysis of brain MRI. This study investigated the changes of cerebral glucose metabolism in patients with narcolepsy.
Methods: Twenty-one patients with narcolepsy and 21 age-matched normal subjects underwent 18F-fluorodeoxy glucose positron emission tomography (FDG-PET). The SPM-99 was used for image preprocessing and statistical analysis. All images of 21 patients and 21 controls were spatially normalized into standard PET template with 12-parameter affine transformation. Spatially normalized images were smoothed by convolution with an isotropic gaussian kernel with 14-mm full width at half maximum to increase signal to noise ratio. To remove the effect of the global metabolism, the count of each voxel was normalized to the total count of the brain using proportional scaling. t-test was used for group comparison between narcolepsy patients and normal subjects. The significance level was set to false discovery rate (FDR) corrected $p < 0.05$, and the extent threshold was set to $k > 50$.
Results: The reduced glucose metabolism was observed in bilateral rectus and inferior frontal gyri, left superior frontal gyrus, and bilateral medial parietal gyri of patients with narcolepsy at uncorrected $p<0.001$. But the significances of hypometabolism in those brain regions were marginally non-significant at the false discovery rate (FDR) correction for the multiple comparison problem ($p=0.057$). No significant changes of glucose metabolism was found in hypothalamic region at the uncorrected $p<0.001$. Although the small volume correction according to predefined hypothesis was applied with the spare of 15 mm radius (center point; s, y, z = 0, -9, -13), the hypothalamus failed to show significant metabolic changes.
Conclusion: The SPM analysis of FDG-PET between narcolepsy patients and normal subjects showed no hypometabolism in hypothalamus, but hypometabolism in bilateral rectus and inferior frontal gyri, left superior frontal gyrus, and bilateral medial parietal gyri.

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The Month of Birth Pattern in Narcolepsy is Moderated by Cataplexy

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Introduction: A March peak and a September trough in the birth pattern of narcolepsy patients with cataplexy has recently been demonstrated in a study that utilized three different geographic cohorts (Dauvilliers et al., 2003). The present study addressed three questions. First, would this month of birth pattern replicate in another sample? Second, does this month of birth pattern change depending on the presence and severity of cataplexy? Third, are a March birth (yes/no) and HLA-DQB1*0602 status (yes/no) independent risk factors?
Methods: Data were obtained from 530 narcolepsy patients taking part in a multi-site clinical trial assessing the safety and efficacy of modafinil in the treatment of the sleepiness associated with narcolepsy. All diagnoses were made according to the International Classification of Sleep Disorders and based on clinical histories, nocturnal polysomnography, and a Multiple Sleep Latency Test. All month of birth analyses employed

general population values from the National Center of Health Statistics as the comparison group. Analyses conducted according to cataplexy severity split the above patient group into those without cataplexy (n=94), with mild cataplexy (n=223), moderate cataplexy (n=172), or severe cataplexy (n=41). These severity ratings were based on clinical judgments at disease onset and at the time of enrollment in the study. To examine the potential combined effect of a March birth and HLA-DQB1*0602 status, a hierarchical logistic regression was performed to assess the significance of the interaction odds ratio.

Results: For all 530 patients including those without cataplexy, March was the month with the most births (12.3%) and September was the month with the least births (7.0%). When analyzed across cataplexy by individual month, the percentage of March births was significantly higher than the comparison value only for patients with moderate cataplexy (16.3%, chi-square=15.2, p<.0001) or severe cataplexy (22.0%, chi-square=12.9, p<.001) while the percentage of September births was lower than the comparison value only for patients with moderate cataplexy (3.5%, chi-square=5.9, p<.05). The hierarchical logistic regression yielded a non-significant interaction odds ratio between a March birth and HLA-DQB1*0602 status (OR=0.82, chi-square=0.06, p=.81).

Conclusion: A March birth is a risk factor for narcolepsy only for patients with moderate or severe cataplexy. This risk factor has more specificity to cataplexy than the HLA polymorphism since narcolepsy patients without cataplexy still display a higher percentage of the polymorphism compared to the general population. The interaction analysis revealed that a March birth (yes/no) is acting as a risk factor independently of HLA-DQB1*0602 status (yes/no). These risk factors may act in an additive fashion to increase the overall liability for developing narcolepsy. Surveillance data indicates that a peak in rhinovirus infections occurs in September or October. The March peak in narcolepsy births may thus be a function of exposure to a maternal rhinovirus infection during the second trimester, which is a sensitive period of fetal neurodevelopment.

Data made available by Cephalon, Inc.

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Cross-Sectional Assessments of Body Weight in Two Hypocretin/Orexin Deficient Mice Models Housed in the Same Environment

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Introduction: Increasing evidence has suggested that narcolepsy is not a simple sleep disorder, but abnormalities in energy homeostasis, autonomic nerve and neuroendcrine functions associated with loss of hypocretin/orexin signaling, also underlie its pathophysiology. Obesity in human narcolepsy has been reported for several decades, but this is prominent only in a subset of narcoleptic patients and the exact mechanism of the obese tendency in narcolepsy is not yet known. Two recent studies have also suggested that plasma leptin levels are lower in human narcolepsy compared to age, gender and body weight mass index-matched controls, suggesting the involvement of insufficient leptin signaling in hypocretin-deficient narcolepsy. Hara et al. previously reported that orexin/ataxin-3 transgenic (TG) narcoleptic mice (C57BL6/25% DBA, N2) became obese around 8 to 10 week old and became significantly heavier than wild type [WT] littermates from 14 week old, while narcoleptic mice ate less during this period, suggesting the importance of hypocretin signaling in food intake and energy homeostasis. In the current study, we have assessed the body weight of two narcolepsy mice models, namely preproprexin gene knockout (KO) and orexin/ataxin-3 TG mice (and respective WT mice housed in the same environment), as well as leptin levels in a selected population of TG and WT mice.

Methods: The breeding pairs of N3-4 generations (backcrossed with C57BL6) of TG /- (C57BL6/DBA) and KO (C57BL6J-129/SvEV) mice arrived in April 2002, and the breeding was initiated at the Stanford Center for Narcolepsy. All mice were fed with regular rodent oval pellets (Prolab RMH 3000, PMI Nutrition International). In August 2003, the weight of N3-5 (backcross to C57BL6) mice in the colony were recorded (121 homozygous KO, 151 heterozygous [Hz] KO, 100 wild type [WT] mice for KO group, 211 TG, and 139 WT mice for TG group), and the weight, age and genotype of the mice were analyzed with a cross-sectional design. In a selected population of TG (n=57) and respective WT (n=45) mice aged between 101 to 200 days, had their blood collected transcardially to examine serum leptin levels. All blood samples were collected between 9:00 and 11:00 for the genotype comparison.

Results: As previously reported by Hara et al., the weight of TG mice became heavier than WT mice in each gender around 80 days old, and this tendency was observed for mice up to 200 days old. Interestingly, an obese tendency (vs. WT in the same gender) was more prominent in female TG mice than male TG mice. We have also observed that the body weight of KO mice from around same age become heavier than the respective WT mice, and heterozygous animals exhibited intermediate body weight in each gender. As seen in TG mice, an obese tendency in female KO is more prominent than male KO mice. Serum leptin levels were significantly correlated with body weight of animals and significantly higher in narcoleptic mice in both males (11.2±1.8 ng/ml [mean weight=32.7g] vs.9.3±1.7 ng/ml [30.4g]) and females (14.8±1.6 ng/ml [26.5g] vs. 4.7±0.3 ng/ml [22.1g]). This tendency was observed even when levels in matched body weight groups in each genotype were compared.

Conclusion: Both hypocretin/orexin-deficient TG and KO (hypocretin/orexin cell death vs. ligand deficit model) became obese at a similar age. Taken together with the results that Hz animals (reported to produce 75 % of hypocretin-1 of WT mice) exhibited the intermediate phenotype, it is likely that the obese tendency observed in these mice in our housing facility was dependant on the hypocretin/orexin deficiency status. Obesity may also depend on the maturation and gender of the animals. In contrast to the human studies, we observed increased blood leptin levels, and a leptin resistant obesity was suggested in these narcoleptic mice. Finally, the narcoleptic mice models are very useful to study the roles of hypocretin/orexin in energy homeostasis, and further studies in these animals are warranted.

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Effects of Tyrosine Supplement and Acute Tyrosine/Tryptophan Depletion on Cataplexy in Canine Narcolepsy

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Introduction: Approximately 95% of narcoleptic subjects are currently treated using wake-promoting and/or anticataplectic medications. The most widely used anticataplectic medications are monoamine reuptake inhibitors (i.e., antidepressants). These enhance central serotonergic and adrenergic neurotransmission. Interestingly, some authors have reported that tyrosine supplementation (one of the essential amino acids and a precursor of catecholamine [CA], dopamine and norepinephrine), reduces daytime sleepiness and cataplexy in some human cases. Narcoleptic subjects often have dietary preferences, and selective effects

of certain foods on their symptoms were reported. In this study, we evaluated the effects of tyrosine supplementation and acute tyrosin/tryptophan depletion (a manipulation known to decrease brain serotonin [5-HT] and CA synthesis) on cataplexy using the canine model of narcolepsy. Tryptophan depletion has recently been reported to rapidly aggravate depressive symptoms in patients with depression, especially when treated with serotonin reuptake inhibitors.

Methods: Six narcoleptic Dobermans were used. The effects of cataplexy were assessed using the Food Elicited Cataplexy Test. After 3 days of baseline cataplexy testing, L-tyrosine (3g/dog) was administered for 16 consecutive days. Cataplexy testing was carried out daily during administration and on the 1, 2, 3, 7 and 15 days after the cessation of the treatment. Acute tyrosin/tryptophan dpletion was carried out using a mixture of amino acid (L-alanin 1.8g, L-arginie 1.6g L-cysteine 0.9g, glycine 1.0g, L-histidine 1.0g, L-isoleucine 2.0g, L-leucine, 4.5g. L-lysine 3.6g, L-methinine 1.0g, L-phenylalanine 1.8g, l-proline 3.9g. l-serine 2.2g, l-threonin 2.3g, l-tryptophan 0.8g l-tyrosin 2.2g, l-valine 2.9g), with or without trypthophan (Tryp-D) or phenylalanine and tyrosine (Phe/Tyr-D). Tryp-D administration is known to induce a rapid (5-hour) and substantial (80% to 90%) lowering of tryptophan in plasma and tissues (and also reduces the rate of brain 5HT synthesis). Similarly, the dietary availability of tyrosin has been reported to affect brain catecholamine synthesis. The time course effects of Tryp-D and Phe/Tyr-D on cataplexy were also evaluated during the drug free period and while the animals were chronically treated with desipramine (NE uptake blocker) and clomipramine (5HT and NE uptake blocker).

Results: Tyrosine supplementation had no effect on cataplexy. Tryp-D, and Phe/Tyr-D slightly aggravated cataplexy during the drug free period (but these effects did not reach statistically significance). Two weeks of desipramine and clomipramine administration significantly reduced cataplexy (-73 % [from the baseline] and -48%, respectively). We found that Tryp-D and Phe/Tyr-D partially but significantly reversed the anticataplectic effects of desipramine (-29 % [from the baseline] by Tryp-D and -43 % by Phe/Tyr-D) and clomipramine (-10 % by Tryp-D and -33 % by Phe/Tyr-D).

Conclusion: Whether or not tyrosine supplementation is effective in treating narcolepsy has been controversial. Two long-term administration uncontrolled studies have reported positive effects while one double blind short-term administration study did not. In our study, supplementation of tyrosine, has had little effect on cataplexy in a canine model. These results are consistent with our previous finding that L-Threo-DOPS (a direct synthetic precursor of NE), had no effects on cataplexy, and suggested that the administration of catecholamine precursor is not a viable therapeutic avenue for narcolepsy. Interestingly however, our results also indicate that the lowering of 5HT and CA synthesis during antidepressant treatments may aggravate cataplexy.These findings suggest that diet or nutrition may have a modulatory effect on the severity of cataplexy in patients treated with anticataplectic medications.

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Use of Sodium Oxybate in Veterans with Narcolepsy

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Introduction: Sodium oxybate is a novel compound that was approved by the Food and Drug Administration in 2002 for use in cataplexy in narcolepsy. There is data to suggest efficacy of sodium oxybate in other symptoms of narcolepsy as well. The purpose of this study was to examine the efficacy of this medication in the common symptoms of narcolepsy in a cohort of veterans of the American military.

Methods: This was an open-label study conducted at the Veterans Affairs Medical Center, Durham, NC. All patients with narcolepsy to whom sodium oxybate was prescribed were included in this analysis. The dose and duration of use of sodium oxybate for each patient were noted. Prior to starting the medication, patients were asked to complete the Epworth Sleepiness Scale (ESS). In addition to the ESS, patients also were asked to rate their cataplexy, hypnogogic hallucinations, sleep paralysis, and nocturnal sleep on a Likert scale, with 1 being the best possible and 9 being the worst possible. The ESS and these questions were posed to the patients again on December 1, 2003. The means of the ESS and cataplexy, hypnogogic hallucination, sleep paralysis, and nocturnal sleep scores were compared using Students t-tests. Concomitant medications were not altered.

Results: Eighteen patients with narcolepsy were prescribed sodium oxybate. After initially agreeing to try the medication, 5 patients had not tried it. One patient discontinued the medication due to excessive daytime side effects. Twelve patients used sodium oxybate for a mean of 6.2 (± 2.8) months at a dose of 6.1 (± 1.4) gm/night. Prior to use of sodium oxybate the mean ESS score was 18.4 (± 4.0) and after use the score was 9.7 (± 4.8, p=0.001). The before and after cataplexy scores were 7.3 (± 2.0) and 2.3 (± 1.7, p=0.00001); hypnogogic hallucination scores were 7.4 (± 1.5) and 4.0 (± 2.6, p=0.01); sleep paralysis scores were 7.1 (± 2.7) and 1.6 (± 0.9, p=0.006); and the nocturnal sleep scores were 7.4 (± 1.4) and 3.8 (± 2.4, p=0.0005), respectively.

Conclusion: Sodium oxybate has efficacy not only in decreasing cataplexy, but also improves daytime sleepiness, hypnogogic hallucinations, sleep paralysis, and nocturnal sleep. These effects were seen in veterans with narcolepsy, a group with typically more severe symptoms; others with narcolepsy are likely to show similar improvement. Despite education about the benefits and potential side effects, 28% of patients did not use sodium oxybate even once. Even closer follow-up and more patient education may be needed to ensure compliance.

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Descriptive Mapping of Orexin in the TAIEP Rat

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Introduction: We have been studying a myelin mutant rat in our laboratory, characterized by tremor, ataxia, immobility, epilepsy, and paralysis (taiep). Sleep is disturbed in these rats, with significantly reduced paradoxical sleep (PS) (Anch & Laposky, 2000), as well as decreased slow wave sleep and increased arousals (Prieto et al., 1991). Interestingly, Prieto et al. also reported characteristic “sphinx” position that sometimes occurs during PS, in which the animals show increasing muscle tension (EMG), with slow rotation of the head. These sleep disturbances and increasing tonicity during PS mimic some clinical sleep disorders. In particular the sleep stage profile is similar to Narcoleptic sleep, with possible brainstem involvement characteristic of REM Behavior Disorder. Since Orexin is a neuropeptide that controls sleep and waking mechanisms and is known to be reduced in Narcolepsy, we mapped whole brain orexin levels in these animals.

Methods: Three groups of 10 rats each; control, taiep, and a heterozygous taiep rat were examined Each group was aged matched for 6 months. Tissue was labeled with orexin (CalBioChem, 1:3000) primary antibody. Product was visualized with DAB and glucose oxidase. Two computer programs were used for measurement. StereoInvestigator was used to obtain a count of orexin producing cell bodies and NeuroLucida was used to map out and determine the volume of projection fibers and terminals. Data were statistically analyzed using the Mann-Whitney U test.

Results: An increase of cell bodies in the lateral hypothalamus is present in the taiep rats in comparison to normal rats, however, not statistically significant (U = -0.791, p = .429).

Conclusion: We conclude that the characteristic disturbed sleep pattern exhibited in taiep rats does not seem to be mediated by orexin.

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Sodium Oxybate Post-Marketing Evaluation Program: Results From The First 12 Months

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Introduction: On July 17, 2002 Xyrem® (sodium oxybate oral solution, Orphan Medical, Inc., Minnetonka, Minnesota) was approved in the United States for the treatment of cataplexy in patients with narcolepsy. Considering the small number of patients with cataplexy, this approval was granted with data from approximately 500 patients in the clinical trials. As a result, a post-marketing surveillance program was required to collect data on 1,000 patients to expand the safety profile to the 1500 patient population recommended by ICH guidelines. Orphan Medical initiated the Post Marketing Evaluation Program (PMEP) to solicit and capture such safety data from these patients.
Methods: All sodium oxybate prescribers must first register through a central pharmacy. The registration process provides the prescribers with materials which include PMEP forms that facilitate solicitation of safety data from the patients after a recommended three and six months of therapy. The forms query for events of special interest, as well as any other medical events or symptoms experienced by the patient. The completed forms are faxed or mailed to an independent agency that performs pharmacovigilance services (Drug Safety Alliance, Durham, NC). All PMEP forms returned through October 31, 2003 were reviewed. During that period 358 completed forms were received. Incidence rates were calculated based on that number (n = 358).
Results: Sodium oxybate prescriptions were delivered to a total of 2296 patients as of October 31, 2003, 1538 of whom potentially completed three months of therapy (prescriptions were delivered prior to July 31, 2003). The 358 PMEP forms received represent a total of 245 unique patients (a 16% response rate). Analysis of the data reported on the PMEP forms revealed that greater than two-thirds (69%) of the forms received reported No Adverse Event. Furthermore, all of the events of special interest were reported at lower incidence than expected (clinical trial results in parenthesis): vomiting 3% (8%); incontinence 4% (8%); sleepwalking 2% (7%); confusion 4% (7%); convulsions 0% (3%).
Conclusion: Twelve months of safety data from commercially-available sodium oxybate was collected through a solicited, post-approval surveillance program. Evaluation of that data has shown the adverse events of special interest, which were specifically queried on the form by direct questioning, were all reported with a lower incidence than occurred during the clinical trials. There was some initial concern that physicians would only complete a PMEP from to report an AE, and would not respond to report "no AE". In fact, 69% percent of the forms received reported "no AE", significantly higher than the 18% of patients in the integrated trials who reported no AE. A response rate of 16% for a voluntary reporting program is commendable; however, physicians are encouraged to return a completed PMEP form for every patient at three and six months of therapy, whether there has been an adverse event or not, to compile as complete a safety profile as possible.

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12-Month Evaluation Of A Novel Risk Management Program For Responsible Distribution Of Sodium Oxybate Treatment For Cataplexy

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Introduction: Xyrem® (sodium oxybate) oral solution, indicated as a treatment for cataplexy in patients with narcolepsy, was approved by the FDA in conjunction with a Risk Management Program in July 2002. The active ingredient, sodium oxybate, is also known as GHB, a drug with a history of abuse. The Risk Management Program was designed to maximize physician and patient education about the safe use of sodium oxybate and minimize potential diversion or abuse of the approved drug by limiting distribution through a central pharmacy. The ability of the Risk Management Program to limit diversion was evaluated following the first 12 months of commercial use beginning October 1, 2002.
Methods: Four tools are employed to evaluate the effectiveness of the Risk Management Program in preventing diversion, defined as utilizing an otherwise legitimate product for an unlawful use: (1) Prescribers are proactively sent Post-Marketing Evaluation Program forms and requested to report "inappropriate use" of sodium oxybate at months 3 and 6 of treatment, including premature refill requests, reports of theft or loss, difficulty in using or preparing drug and "other" inappropriate use; (2) Prescriber credentials are verified prior to filling a prescription; additionally, the pharmacy maintains a registry of all valid prescribers. (3) The central pharmacy confirms delivery of each sodium oxybate shipment and reports theft, loss or other spontaneous reports of potential diversion; (4) A system is also in place for receiving and documenting spontaneous complaints or safety issue.
Results: By September 30, 2003, prescriptions had been filled for 2021 patients, and 334 Post-Marketing Evaluation Program reports were submitted for 228 unique patients. There were no reports of inappropriate use. The screening of physician credentials resulted in the pharmacy declining registry of six physicians. Four Diversion Risk Reports included the reported theft of product from a patient's car; report of non-delivery because a prescription delivery was left at a patient's doorstep due to courier error; a bottle was inadvertently left at a hotel while traveling; and a hospital pharmacy lost a sodium oxybate supply bottle while a patient was hospitalized for an unrelated stay. There was one case of accidental overdose and one incident of possible withdrawal syndrome was reported; however, in that case the reporter was unclear if the withdrawal symptoms were due to sodium oxybate, anticholinergic (diphenhydramine) toxicity or both.
Conclusion: The Risk Management Program was designed to encourage safe use of sodium oxybate through physician and patient education while taking steps to minimize the risk for diversion. There have been no reports of actual diversion through the Risk Management Program, although there were thirteen cases of potential diversion. At this time it appears that the goals of the program are being met.

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The Occurrence of Cataplexy in Relation to Proceeding REM Sleep

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Introduction: Cataplexy is not only one of the most disabling symptoms of the narcolepsy syndrome, but also the most specific symptom as a predictor for the HLA-associated hypocretin deficiency syndrome. In contrast, other REM-sleep related symptoms seen in narcolepsy, such as hypnagogic hallucinations and sleep paralysis, also occur in association with other sleep disorders or even in control subjects. Although cataplexy is phenotypically similar to REM sleep atonia, some differences with REM sleep have also been noted. The occurrence of cataplexy is not affected by the ultradian REM sleep cyclicity, and cataplexy can be elicited at anytime by emotional excitation when the animal is awake. Furthermore, sulrpiride (a dopamine D2/3 antagonist), suppresses cataplexy in canine narcolepsy, but does not reduce REM sleep in the same animals, suggesting that the mechanisms for triggering cataplexy are at least partially distinct pharmacologically from those triggering REM sleep. In this study, we have examined whether the amount and timing of preceding REM sleep or slow wave sleep (SWS) may affect the occurrence of cataplexy in narcoleptic Dobermans.
Methods: Four narcoleptic Dobermans implanted with polygraph recording electrodes were used. The dogs were left alone in the recording room in the afternoon (1:00 to 5:00 pm), and their sleep was monitored polygraphically for 20 to 30 minutes. Sleep amounts and sleep stages were evaluated in a total of 74 sessions. SWS was observed in 73 sessions, REM sleep (plus SWS) in 44 sessions. Immediately after every sleep recording session, an experimenter came into the recording room and tried to initiate cataplexy for 10 minutes (using the presentation of appetitive food). The occurrence of cataplexy (starting time, number of attacks and duration) was recorded. The latency to the first cataplectic attacks, the duration of the first attack as well as the total time spent in cataplexy (TSC) in 5 minutes period were used for the analysis. Sleep prior to cataplexy testing was scored visually for every 30 second epoch, and the total amounts of wake, SWS, and REM sleep in 5, 10 and 20 minutes before the cataplexy testing was calculated. Cataplexy and prior sleep data were correlated using Pearson's correlations.
Results: The occurrence of cataplexy (TSC) in the 5-minute period of the test was negatively correlated with amounts of REM sleep (but not SWS and wake) observed during 10 ($p=0.008$) and 20 ($p=0.02$) minutes sleep recording sessions prior to cataplexy testing. REM sleep amount in the 10 and 20 minute proceeding periods were also significantly correlated with the latency to the first cataplexy attacks (positively) and the duration of the first cataplectic attacks (negatively). The correlation REM sleep in the proceeding 10 minutes was the most significant among the 5, 10 and 20-minute time bins.
Conclusion: The occurrence of cataplexy is influenced by prior REM sleep amounts. Narcoleptic dogs are resistant to having cataplectic attacks when REM sleep has occurred 10 to 20 minutes prior to the cataplexy testing. In addition to our previous data suggesting that the mechanisms of triggering cataplexy are different from that of REM sleep, the current results indicate shared pathophysiological mechanisms between cataplexy and REM sleep. Recent human and animal studies have demonstrated that the occurrence of cataplexy, but not other REM related symptoms, is tightly associated with a chronic loss of hypocretin signaling. Cataplexy is thus a unique pathological condition and is likely distinct from physiological REM sleep atonia. Nevertheless, our results also indicate that short-term feedback mechanisms resulting from the occurrence of physiological REM sleep on cataplexy also exists. Additional work is needed to further elucidate the mechanisms/pathways involved in the triggering of cataplexy versus REM sleep.

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Evaluation of Modafinil Dosing During Long-term Treatment of Narcolepsy and Obstructive Sleep Apnea

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Introduction: Modafinil is a novel wake-promoting agent that effectively improves wakefulness in patients with excessive sleepiness associated with several dyssomnias. Modafinil is approved for improving wakefulness in patients with narcolepsy. Clinical trials also demonstrated its utility (at 200 mg and 400 mg) as an adjunct treatment in patients with residual excessive sleepiness associated with obstructive sleep apnea (OSA). The dose of modafinil necessary to sustain wakefulness may relate to the underlying excessive sleepiness severity. Patients with narcolepsy are usually sleepier than nCPAP-treated patients with OSA. We report here results of a meta-analysis of open-label extension studies to determine whether the dose necessary to optimize wakefulness differed between these two populations.
Methods: Patients with narcolepsy or residual excessive sleepiness associated with nCPAP-treated OSA who had completed 1 of 3 randomized, double-blind, placebo-controlled studies entered the open-label extension phases. In the extension studies, dosing was flexible (200–400 mg per day) based on clinically judged efficacy and tolerability. Study durations were 40 weeks for both narcolepsy studies and 12 months for the OSA study. Analyses were conducted using the average dose during extension period. Modafinil's effect on excessive sleepiness was assessed using the Epworth Sleepiness Scale (ESS). Adverse events were recorded.
Results: 744 patients received modafinil in open-label studies (n=478, narcolepsy and n=266, OSA). 84% of patients completed the studies (n=453 [95%], narcolepsy and n=175 [66%], OSA). Baseline excessive sleepiness, assessed by the mean (±SD) ESS, was 17.4±4.1 in narcolepsy versus 14.5±3.6 in OSA ($p\leq.001$). Mean (±SD) body mass index (BMI) was 28.8±6.3 kg/m2 in narcolepsy patients versus 36.2±7.6 kg/m2 in OSA patients ($p<.0001$). The change from baseline of ESS at endpoint was -4.5±4.7 for OSA and -4.4±4.9 for narcolepsy. Half of all patients with narcolepsy studied were in the 400 mg average dose group, 34% were in the 300 mg average dose group, and 16% in the 200 mg average dose group. By comparison, 33%, 43%, and 24% of patients with OSA were in the 400 mg, 300 mg, and 200 mg average dose group, respectively. Notwithstanding greater BMI among patients in the OSA studies, these patients titrated to significantly lower doses of modafinil to achieve equivalent efficacy indexed by ESS. Modafinil was well tolerated and adverse events were similar in both patient populations.
Conclusion: When titrated for both efficacy and tolerability, a greater percentage of patients with narcolepsy were treated at higher doses of modafinil than nCPAP-treated OSA patients with residual excessive sleepiness. This difference may relate to differences in excessive sleepiness at baseline.

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Hypocretin Immunoreactivity in the Blood of Genetically Engineered Narcoleptic Mice Models

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Introduction: Undetectably low CSF hypocretin-1/orexin A level is a very specific finding in narcolepsy-cataplexy. As a result, CSF hypocretin-1 measurements are increasingly used as a diagnostic test for human narcolepsy. Because CSF taps are invasive, a blood test for hypocretin deficiency would be preferable, providing peripheral hypocretin abnormalities are also observed in narcolepsy. However, hypocretin-1 is not consistently found in human blood. Previously reported levels of immunoreactive [IR] hypocretin-1 vary significantly from laboratory to laboratory, with reprted values being close to the detection limits. In contrast to humans, rodents have relatively high IR hypocretin signals in the blood. Well-established hypocretin deficient narcoleptic models are also available (i.e., preproorexin knockout [KO] and orexin/ataxin-3 transgenic narcoleptic mice) in these species. In this study, we have determined whether hypocretin deficiency can be detected in the blood of these narcoleptic models.

Methods: Blood samples (300 to 500 µl) were collected transcardially, and serum hypocretin signals were measured using radioimmunoassay (RIA) without prior extraction. A rabbit anti-hypocretin-1 polyclonal antibody with high sensitivity (IC90 = 4 pg/ml) was developed in-house and used. A pilot study using 40 heterozygous KO mice indicated no differences in blood hypocretin measurements between morning and evening hours. Eighty-two percent of the animals tested had levels above the detection limit during the daytime. Blood samples were therefore collected from KO (n=23) and their wild type (WT) (n=21), and TG (n=100) their WT (n=68) mice between 9:00 and 11:00 am. All mice were derived from founder animals backcrossed to C57BL6 mice (generation N3-N7) at the Stanford Center for Narcolepsy. Additionally, blood samples from 28 WT mice (C57BL6) housed in the same facility were collected and included in the WT control group (96 total) to match the number of TG animals.

Results: Hypocretin levels were similar in the three WT subgroups (KO , TG and C57BL6) and in males versus females. Blood hypocretin levels did not correlate with age or weight in WT mice. Blood hypocretin levels were significantly lower in both KO (26.1±3.0 pg/ml vs. 36.3±2.6 [SEM] pg/ml, p=0.015) and TG (17.6±1.6 pg/ml vs. 35.8±1.8 pg/ml p<0.0001) narcoleptic mice compared to their respective WT mice group. Most strikingly, 30 out of 100 TG mice had undetectably low blood hypocretin levels, while only 1 of 96 WT mice showed undetectable levels (21 % of TG mice overlapped with the mean-2SD of control level). The specificity of undetectable blood levels in TG mice was high (99%), although sensitivity was 30 %. Notably, the overlap in hypocretin values between KO and WT mice (39 % of KO mice overlapped with the mean-2SD of control level) was larger than that of the TG mice comparison. Four out of 23 KO mice and 3 out of 21 WT mice showed undetectable blood hypocretin levels.

Conclusion: Mouse blood hypocretin-1 signal as detected using an RIA with our polyclonal antibody, likely reflects, at least in a large part, a genuine hypocretin signal. Hypocretin deficiency was detected using this method in two different hypocretin deficient narcoleptic mice models (gene vs. cell targeting model). Although it is unknown if peripheral hypocretin deficiency is present in the orexin/ataxin-3 TG narcoleptic mice, one can assume that hypocretin production is absent in the peripheral organ (and brain) of the hypocretin KO mice. The overlap in blood IR hypocretin signals observed between KO and WT mice is likely due to background noise and cross reactivity with non-hypocretin substances. Further experiments aimed at reducing the background (by applying larger sample volumes and the extraction procedure, or by developing higher sensitivity and specificity assays), are needed. Applying this procedure to humans may also in time be useful in diagnosing narcolepsy.

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Hypersomnia Secondary To Hypothalamic Damage And CSF Orexin-A Level In Four Cases

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Introduction: There is an absence or low levels of orexins in the cerebrospinal fluid in a majority of patients with narcolepsy-cataplexy, a chronic sleep disorder characterized by excessive daytime sleepiness and cataplexy. Orexin deficiency has been reported in several symptomatic cases of narcolepsy or hypersomnia associated with neurodegenerative, surgical, ischemic and post-infectious insults to hypothalamus. Here we report patients with hypersomnia secondary to hypothalamic damage and CSF orexin-A level.

Methods: Orexin-A concentration in the cerebrospinal fluid was measured using RIA method reported before by Nishino S (2001),in four cases, in whom the patients had hypersomnia or excessive daytime sleepiness secondary to hypothalamic damage. The diagnoses were hypothalamic tumor in one case, bilateral medial thalamic infarction in two cases, and multiple sclerosis in one case. Orexin-A level was measured in various time courses and the patients were assessed neurologically.

Results: Case 1. A 66-year-old woman reporting symptoms typical for EDS for 1 month. Her time orientation was disturbed and she scored 21/30 on minimental state examination. Her upper extremities showed typical of asterixis. An orexin-A concentration measured 62 pg/ml. Magnetic resonance T2 weighted images of brain showed consistent with hypothalamic tumor. A morning polysomnogram demonstrated REM sleep latency of eleven minutes with five minute sleep latency. Case 2. A 45-year-old man admitted to hospital with chief complaint of disturbed consciousness. MRI examination disclosed the cause of hypersomnia as bilateral medial thalamic infarction. His symptoms were alleviated for 2 months course but he cannot work because of decreased motivation for work and memory disturbance. Orexin-A concentration measured 322 pg/ml in acute stage and 255pg/ml in chronic stage. Case 3. A 75-year-old man was another such case but was more severe because in two months course he open eyes only when he was stimulated by roud voice or pain and complicated by hemiplegia and he cannot speak. But he can obey simple orders. Orexin-A concentration measured 170 pg/ml in acute stage and 148pg/ml in chronic stage. Case 4. The patients was a 31-year-old woman who had been diagnosed as having multiple sclerosis. She became sleepy and admitted. She showed symptoms of hypothermia, bilateral Horner syndrome, excessive sleep, and memory disturbance. Orexin-A concentration measured 103 pg/ml in acute stage and 51pg/ml in three months later. But she was recovered well.

Conclusion: Compared to controls (280+/-33pg/ ml), orexin A concentration in CSF showed marked decrease in two cases where each patient had hypothalamic tumor and MS plaque. On the other hand one case with bilateral medial hypothalamic infarction showed relative reduction

and in more milder case there was not reduction. There might be some differencies between direct damage on the hypothamus and bilateral medial thlamic infarction.

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Affective Startle Reflex Modulation In Patients With Narcolepsy-Cataplexy

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Introduction: Cataplexy is typically triggered by emotions suggesting the possibility of an abnormal emotional motor control in narcolepsy-cataplexy (NC). To assess emotional control of efferent motor pathways in NC patients we test muscle response of acoustic startle reflex (ASR) during affective stimulation. In healthy subjects ASR covaries with emotional valence of stimulus perception.
Methods: In seven NC-patients and three healthy matched controls (HS) we measured the magnitude (area under the curve) of acoustic elicited OOR (orbicularis oculi reflex) during the presentation of positive, neutral and negative pictures taken from the standardized International Affective Picture System (IAPS)
Results: In three NC-patients (=43%) muscle responses were too small to assess emotional modulation. In the remaining four NC-patients emotional modulation of ASR was different when compared to normal controls. During pleasant pictures responses in HS were attenuated (92% +/- 14% of neutral picture response, range: 76-101%) whereas it was comparable to neutral response in NC (100% +/- 37% of neutral picture response, range: 66-163%). During unpleasant stimuli responses were enhanced in healthy controls (HS: 142% +/- 28% of neutral pictures, range: 117-173%; NC: 124% +/- 46 of neutral pictures, range 82-192%) but attenuated in NC-patients (95% +/- 12% of neutral pictures, range 87-113%)
Conclusion: Preliminary results suggest that motor response to emotional pictures is abnormal in NC. Assessment of emotional modulation of ASR in NC may represent a useful tool for the diagnosis of cataplexy.

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Effectiveness and Patterns of Methamphetamine Use in Narcolepsy Patients

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Introduction: Narcolepsy is a neurological condition characterized by excessive daytime sleepiness (EDS) and cataplexy. Although lack of hypocretin (orexin) in CNS has been found in most patients, the exact cause remains unknown and no curative treatment is available. At the current time, symptoms such as EDS and cataplexy are treated with combinations of stimulants and other medications. Methamphetamine is a potent stimulant causing neuronal release of monoamines. In a study by Mitler, et al in 1993, use of methamphetamine resulted in a significant decrease in daytime sleepiness. However, methamphetamine has not been approved by FDA for treatment of narcolepsy. In this study, we analyzed survey data to investigate patterns of methamphetamine use in narcolepsy patients.
Methods: Surveys were sent to narcolepsy patients in a large cohort from the Stanford Center for Narcolepsy. Of 473 surveys mailed, 342 were received, and 298 were completed (a completion rate of 87%). The surveys gathered information about current or past use of methamphetamine, dosage and frequency, indications, effectiveness, duration of use, reasons for discontinuation, as well as use of other relevant medications. Data from the surveys were compared between the past and the current use group.
Results: Of the 298 patients, 7% (21/298) had been prescribed methamphetamine. Of these, 7 were current users (5 female, 2 male, all Caucasian, mean age 43.6), and 14 had discontinued (8 female, 6 male, 12 Caucasian, 1 African American, 1 Hispanic, mean age 49.4). Daytime sleepiness was the main reason for initial use in both groups (7/7 vs. 13/14, current vs. past, respectively). Other reasons were cataplexy (1/7 vs. 3/14), hypnagogic hallucinations (2/7 vs. 3/14), sleep paralysis (1/7 vs. 3/14), and disturbed sleep (0/7 vs. 3/14). Among the 7 current users, the mean daily dosage of methamphetamine was 50.7 mg (10-125 mg). It was rated either very effective or somewhat effective. Seventy-one percent (5/7) used only methamphetamine, 1 used clomipramine and 1 fluoxetine -both for cataplexy. Current users had tried other medication treatment prior to methamphetamine including: methylphenidate (6), dextroamphetamine (5), modafinil (4), Adderall® (1), pemoline (2), protriptyline (1), imipramine (2), fluoxetine (1), gamma hydroxybutyrate (1), and venlafaxine (1). Most had tried multiple medications previously and the main reasons for discontinuing prior treatments were lack of effectiveness, loss of effect, and/or side effects. For patients who had discontinued methamphetamine, 43% (6/14) now used one medication, 4 required two, 1 required three, and 1 required four medications for control of narcolepsy symptoms. The main reason for discontinuation was side effects (5/14), followed by other reasons (3/14), limited beneficial effect (3/14), never effective (2/14), and becoming less effective (1/14).
Conclusion: These data suggest that while less than 10% of narcolepsy patients had received methamphetamine treatment, in one third of these patients, methamphetamine was effective and well tolerated. Patients reported doing well on predominantly methamphetamine monotherapy. If methamphetamine was discontinued, side effects were the major cause, not lack of effectiveness. We conclude that for a subset of narcolepsy patients, methamphetamine may be an important treatment option, especially when other agents fail.

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Genes Transcripts Relating To The Immune Response Are Up-Regulated In Narcoleptic Postmortem Hypothalamus Using Microarray

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Introduction: Narcolepsy is a sleep disorder that affects 1 in 2000 people. Its main symptoms include excessive daytime sleepiness, loss of muscle tone in response to emotional stimuli (cataplexy), and other abnormalities of rapid eye movement (REM) sleep. We and others have shown that narcolepsy is associated with undetectable levels of novel neuropeptides, the hypocretins/orexins, in the CSF and loss of hypocretin neurons in the brains of patients with narcolepsy. Although narcolepsy is tightly associated with HLA-DQB1*0602, suggesting an autoimmune etiology, it remains to be determined whether the hypocretin neurons in the hypothalamus are actually damaged through autoimmune mechanisms. Furthermore, it is unclear how the absence of hypocretin neurotransmission results in the symptoms of narcolepsy.
Methods: Total 8 controls and 6 narcoleptic postmortem frozen hypothalamic blocks were sliced coronally and hypothalamic area were dissected. Total RNA were extracted from the tissue and 5-8 microgram of them were used for the following procedures according to the GeneChip expression analysis technical manual from Affymetrix. We used MicroArray Suite5.0 software, Cluster and Treeview, Significant Analysis of Microarray from Stanford and other publicly available data

mining softwares for the data analysis.
Results: We showed that hypocretin transcripts were down-regulated in narcolepsy versus control posterior hypothamali. Data obtained using 6 narcolepsy and 5 control brains indicate that transcripts annotated to immune response pathway such as HLA class II, complement components and CD53 are significantly upregulated in narcoleptic anterior hypothalami. Further data analysis is in process.
Conclusion: Our results suggest immune abnormalities in human narcolepsy brain. We also found hypocretin deficiency in the same brains. Further analysis are needed to validate and extend on these observations.
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The Functional Neurobiology Of Narcolepsy

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Introduction: Executive functions such as planning, reasoning, problem solving, response selection / inhibition, short term/working memory, task organization, creativity are dependent on a interactions within a distributed neural network that includes the dorsolateral prefrontal cortex, the anterior cingulate in the medial wall, and the posterior parietal cortex. States of excessive daytime sleepiness such as obstructive sleep apnea and sleep deprivation are associated with executive dysfunction. Working memory is a system used for temporary storage, active monitoring of and manipulation of information, and is a critical executive function. Dopamine is a critical neuromodulator of executive functions, and the orexin system projects to the midbrain dopaminergic systems, the major source of prefrontal dopamine. We hypothesized that narcoleptic would demonstrate vulnerabilities in the executive network.
Methods: Three patients with narcolepsy, (2 with cataplexy, 1 without) and one patient with idiopathic hypersomnia were evaluated. Working memory was probed using a verbal 2-back task, and functional magnetic resonance imaging performed on a 3 Tesla scanner. The task was a block-design, 30 seconds baseline attention task alternating with 1 minute of the working memory task, total duration 9.5 minutes. Multiple runs (2-3) were obtained in each scan session. Data analysis included motion correction, spatial smoothing, linear trend removal and generation of activation maps using a General Linear Model with the Brain Voyager software. Neuroanatomical localization and extent of activation was determined after transformation into a standard stereotaxic space (Talairach). Healthy control data (8 subjects) and obstructive sleep apnea data (16 subjects) from separate protocols were available to compare with narcoleptics.
Results: The following preliminary findings are reported: 1) Untreated narcolepsy may be associated with widespread bilateral activation of prefrontal cortical areas during working memory tasks, greater in spatial extent that healthy controls. This is in contrast to obstructive sleep apnea, where reduced prefrontal activation was seen in the untreated state. 2) Repeated scan runs results in within-session fatigue that is evident by subjective (Karolinska scale) and objective (working memory speed, spatial extent of activation) criteria. 3) Repeated scans, especially in the untreated state, shows a progressive drop out of activation from the prefrontal cortex with relatively preserved posterior parietal activation. 4) The activation map of the single patient with idiopathic hypersomnia showed reduced prefrontal activation. Results from further subjects and path analysis (effective connectivity between nodes of the executive network) will be available by the time of presentation.
Conclusion: Executive function is vulnerable in narcoleptics. The prefrontal cortex demonstrates the maximal change in the functional MRI equivalent of a Maintenance of Wakefulness Test. In this model, functional brain activation demonstrates unique temporal instability on a time-scale of 20-30 minutes. Narcolepsy may be a useful clinical condition to explore the spatiotemporal dynamics of executive functions. Although the results are preliminary, there appear to be differences in the functional neurobiology of different etiologies of sleepiness.

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The Prevalence of Sleep Disturbances in Out-hospital Patients in Lithuania

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Introduction: Sleep problems can be an independent disorder or appear associated with mental or physical disorder and are often a main reason for visiting doctor. From the other side, many somatic or mental disorders are accompanied by sleep disturbances. The purpose of this study was an investigation of prevalence of sleep disturbances in relation to depression and anxiety symptoms as well as quality of life in patients consulting by neurologist or psychiatrist.
Methods: In study were involved 1840 patients at their visits to neurologist or psychiatrist. Patients were collected from 10 different regions covering Lithuania. Each patient completed a questionnaire which consisted Hospital Anxiety and Depression Scale, Pittsburgh sleep quality (PSQ) and SF-36 questionnaires. Sleep disturbances were diagnosed in patients with PSQ index >5.
Results: Up till 65.8% of patients demonstrate sleep disturbances. Among patients with sleep disturbances women (70.5%) prevailed against men (29.5%). Sleep problems were more common with increasing patient's age. PSQI >5 was in 81.3% of patients in 60-69 yr. group vs. 48.5 % of patients in 20-29 yr. group. Only 31.1% of patients did not displayed depression or anxiety symptoms. Depression was found in 4.8% of patients and anxiety in 24.0% of patients. The both symptoms of depression and anxiety displayed 40.1% of patients and women (73.4%) prevailed against men (26.6%). In younger patient's group (20-29 yr.) prevailed anxiety symptoms (28.1%), while depression with anxiety (50.5%) was more characteristic for older group (60-69 yr.). The best sleep quality and psychoemotional status was observed in patients living alone, while divorced or widowers displayed the highest PSQ index and mostly expressed anxiety and depression symptoms. Education level had shown the same tendency. The best sleep demonstrated patients with higher education and the worst one was in patients with primary school education. Worse quality of life was related to worsening sleep quality. Sleep disturbances and depression and anxiety reduced quality of life especially in items of role emotional and role physical functioning. The lowest quality of life was observed in patients with sleep disturbances, having both, depression and anxiety symptoms. The patients reported that in average they slept 7 hours 16 min, but they need 8 hours 28 min. of sleep.
Conclusion: Sleep disturbances were found in 65.8 % of patients consulting by neurologist or psychiatrist. Anxiety and/or depression were found in 2/3 of all patients, especially in women and elderly. Both, anxiety and depression were associated with increased rates of reported insomnia. Quality of life was worse in patients with anxiety and depression reporting insomnia symptoms. The patients reported that they slept 1 hour less than they needed.

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Attribution of Sleep Improvements in Combined Drug and Behavioral Therapies for Primary Insomnia

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Introduction: Attribution of therapeutic gains refers to how a patient explains his improvement. In a context where patients receive both medication and behavioral interventions for insomnia, it has been suggested that sleep improvements would not be sustained over time when patients attribute their initial therapeutic gains to medications alone. In a study investigating the effects of high versus low attribution of sleep improvement to medication, only the low attribution group maintained its sleep improvements after treatment discontinuation. It seems that attributing sleep improvements to medications could undermine self-directed behavioral changes. The present study explored the role of attributions of therapeutic gains in a sequential medication and cognitive-behavioral treatment (CBT) of insomnia.
Methods: Seventeen participants (10 women, mean age 41.6 years) with primary insomnia were included in a multiple baseline across subjects design and randomly assigned to one of the following treatment sequences: (a) medication (zopiclone) followed by Combined (medication + CBT) treatment (Medication->Combined); (b) Combined treatment followed by CBT alone (Combined->CBT); or (c) CBT alone. Participants completed the Attributional Questionnaire (AQ) weekly and daily sleep diaries throughout the 10-week treatment. The AQ includes 3 items, rated on a 0 (not at all) to 100 (extremely) scale, assessing whether one perceives sleep improvement as due to medication, behavior change, or change in beliefs. Sleep Efficiency (SE) and Total Wake Time (TWT) were derived from sleep diaries. Prospective daily and weekly measures were analyzed as within-subject time-series data. Spearman correlations were computed to evaluate the relationships between: (a) sleep of the previous week and attribution of the present week; (b) sleep and attribution of the present week; and (c) attribution of the present week and sleep of the following week.
Results: In the Medication->Combined sequence, previous week's SE and TWT were correlated with the present week's behavior attribution score ($rs = .59$ and $-.61$, $ps < .02$). In the Combined->CBT sequence, correlation between sleep and attribution scores were observed only within the same week ($rs = .41$ and $-.42$, $ps < .02$). In the CBT alone condition, sleep of the previous week was correlated with the present week's behavior attribution scores ($rs = .39$ and $-.42$, $ps < .02$ and $.004$) and medication attribution scores ($rs = -.47$ and $.50$, $ps < .004$). For the two treatment sequences, none of present week's attribution scores were related to sleep of the following week. However, in the CBT alone, both medication and behavior attribution scores were correlated to sleep of the following week (medication: $rs = -.36$ and $.45$, $ps < .004$; behaviors: $rs = .39$, and $-.41$, $ps < .03$).
Conclusion: Despite the intuitive appeal to combining medication and behavioral therapies, concurrent treatment may confuse patients in their attributions of initial therapeutic gains. Patients starting with the combined treatment may not be able to separate the treatment effect due to medications from the effect due to behavior change. Longitudinal follow-ups would be needed to evaluate the impact of this attributional process on long-term outcome.

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Long-term Use of Hypnotics and Sleep Architecture

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Introduction: Approximately 30-35% of adults experiences insomnia at least once a year. Benzodiazepine hypnotics are widely used in this group of patients. There is evidence of altered sleep patterns with the use of benzodiazepines. In contrast non-benzodiazepine hypnotics may restore slow wave sleep and REM sleep in the short term. There is limited information regarding long term use of non-benzodiazepine hypnotics and their impact on sleep architecturel. The aim of this study was to investigate the stability of sleep architecture when hypnotics are used over the long term (more than one year).
Methods: Twelve patients (6 males and 6 females, age 49.75?13.0) diagnosed with insomnia and comorbid periodic leg movements in sleep were treated with benzodiazepine hypnotics. (Group I). Another group of 12 patients (5 males and 7 females, aged 1.0?12.8) diagnosed with insomnia were treated with Imovane 7.5 mg (Group II). Both groups of patients were on these medications for one year. All patients were scheduled for two consecutive overnight sleep studies before treatment initiation and after 1 year of treatment. A single trained scorer blindly reviewed polysomnographic findings according to standardized criteria. Subjective states of sleepiness and fatigue were measured using Stanford Sleepiness Scale (SSS) and Fatigue Severity Scale (FSS).
Results: Following benzodiazepines use there was an expected change in the sleep architecture. Amount of slow wave sleep before treatment was higher than after one year of benzodiazepines use (13.3+/-7.7 vs 5.6+/-5.7, p=.004). Patients from Group I also showed increased level of fatigue on the FSS after one-year use (3.0+/-1.8 vs 4.5+/-1.6, p=0.01). There was no worsening in the daytime sleepiness as judged by the SSS. On the contrary, one-year use of Imovane did not change any parameters of sleep architecture including sleep efficiency, REM sleep and slow wave sleep. No significant differences in subjective levels of daytime sleepiness and fatigue were observed after one-year use of Imovane.
Conclusion: Long-term use of Imovane for treatment of insomnia does not change sleep architecture and does not result in excessive daytime sleepiness and fatigue. Long-term use of benzodiazepines reduces amount of slow wave sleep and increases levels of fatigue.

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The Prevalence Of Insomnia In The Hungarian Population

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Introduction: Although there has been an emerging interest in the epidemiology of sleep problems, very little known about the impact of this problem in Central European countries. We assessed the prevalence of sleep complaints, insomnia in particular, in a nationally representative sample of the Hungarian population.
Methods: "Hungarostudy" is a cross-sectional study enrolling a large nationally representative sample (n=12,643) of the adult Hungarian population at the level of the 150 sub-regions in Hungary. As a door-to-door survey, interviews were carried out between January and June 2002. A battery of questionnaires was administered during a home interview. The Athens Insomnia Scale was used to assess sleep complaints and identify possible cases of insomnia. Additional questions on sleep behavior, as well as questions on current medical therapy for somatic and mental disorders were included in the battery of questionnaires administered. Psychosocial and demographic characteristics were also tabulated.
Results: Forty-seven percent of the sample reported at least one complaint related to sleep and 67% of these subjects complained of more than one sleep symptoms. Based on a cut- off score of 10 or more on the Athens Insomnia Scale, insomnia was reported in 9.2% in the total sample and was about twice as frequent in females compared with males. Sleep deprivation was highly prevalent in the younger and middle-aged groups and it was associated with insomnia. Although the frequency of sleep problems increased with age, it was not increased in elderly people who were otherwise healthy. We found that gender, social status and current somatic and mental disorders were significant independent predictors of sleep disorders.
Conclusion: Sleep complaints and sleep deprivation are frequent problems in the Hungarian population. The prevalence of insomnia in our sample was similar to what has been previously reported from other countries. The high prevalence of sleep deprived individuals warrants further attention.

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Efficacy of a Self-Help Treatment for Insomnia Delivered in the Context of a Larger Community-Based Epidemiological Study

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Introduction: Despite the high prevalence and burden of insomnia for the individuals and society, only a minority of insomnia sufferers receive adequate treatment. Increasing evidence shows that cognitive-behavior therapy is efficacious, well accepted by patients, and produces durable sleep improvements with minimal adverse effects. Nonetheless, such intervention is not widely available and is underutilized in clinical practice. There is a need to validate more readily accessible interventions to reach a larger number of individuals with insomnia. This study evaluated the efficacy of a self-help treatment for insomnia delivered in the context of a larger epidemiological survey.
Methods: The sample consisted of 193 adults (34% of women; age, 18-77, M = 46.1) who were randomly selected from a larger epidemiological study. These participants were offered the opportunity to receive a self-help intervention for insomnia. The severity of their insomnia varied extensively from a complaint without symptom, symptoms without complaint, to a clinical syndrome of insomnia. The only exclusion criteria were working on a night shift and the presence of a sleep disorder other than insomnia. The participants were randomized to a self-help treatment (N = 96) or to a no treatment control group (N = 97). The treatment consisted of six booklets, each covering a component of cognitive-behavior therapy, mailed weekly for a six-week period. All participants kept a daily sleep diary for two weeks and completed several measures before and after treatment. Mixed model analyses were conducted to examine group, time, and group by time interaction effects. The main dependent variables were sleep efficiency, total sleep time, total wake time, sleep quality, sleep satisfaction and the Insomnia Severity Index (ISI) total score.
Results: Results showed significant time effects and no significant group effects for all dependent variables. More importantly, significant

group by time interaction effects were observed for sleep efficiency ($F(1,167) = 18.77$, $p<.001$), total sleep time ($F(1,169) = 5.57$, $p<.02$), total wake time ($F(1,167) = 18.69$, $p<.001$), sleep satisfaction ($F(1,177) = 5.10$, $p<.03$) and ISI score ($F(1,174) = 4.00$, $p<.05$). All sleep variables were significantly improved for the self-help group and remained unchanged for the control group. Improvement rates from baseline to post-treatment were modest, with increases of 4.2% in sleep efficiency and 23.6 min in total sleep time, and a corresponding decrease of 20.7 min in total wake time. Additional analyses conducted as a function of severity subgroups showed that the magnitude of improvement was higher for those with more severe sleep difficulties at baseline.
Conclusion: These results document the benefits of a self-help minimal intervention for insomnia delivered in the context of a large community-based epidemiological study. Longitudinal follow-ups will document the maintenance of those changes and the impact of this educational intervention in preventing more severe sleep disturbances over time.

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The Effects of Distal Limb Warming on Sleep Latency

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Introduction: The purpose of this study is to investigate the functional relationship between sleep and temperature regulation. Are these two functions so intimately linked that an externally produced change in temperature regulation will trigger sleep? The Wirz-Justice group has found that the single best predictor of sleep onset is an increase in the amount of hand and foot warming relative to more proximal areas. Therefore as a next step we wanted to know if an increase in sleepiness would also occur if the distal limbs were warmed through an external manipulation.
Methods: In the current study, five minutes before the participant (N=11) attempted to fall asleep on a multiple sleep latency test nap their hands and feet were immersed in water heated to either 42°C (treatment condition) or water heated to the temperature of the warmest limbs (control condition).
Results: The results showed no significant difference between the warm (M=12.05±4.64) and control (M=11.91±5.1) water conditions ($df=10$, $t=-.13$, $p=0.897$). However, there was a significant decrease in sleep latency between the control ($df=10$, $t=2.48$, $p<0.05$) and warm ($df=10$, $t=2.78$, $p<0.02$) water conditions compared to the initial baseline (M=14.87±3.58) MSLT (no water immersion). Of note, although the greatest amount of warming occurred in the warm water condition, there was also a significant amount of warming in the control water condition.
Conclusion: The results of this study suggest that even mild limb warming can decrease sleep latency compared to a non-water condition. If this finding is correct, this may be used as a behavioral treatment option for individuals with difficulty initiating sleep. Although, because the non-water condition in this study was not counterbalanced the difference found between these groups may simply be the result of an order effect (the baseline condition was not counterbalanced because it was designed to be used to reject subjects from the study who had a mean sleep latency < 10 minutes, therefore it was always the first MSLT performed). Further investigation is required to determine which of these hypotheses is correct.

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No Evidence of Tolerance With Long-Term Non-Nightly Zolpidem Administration in Patients With Primary Insomnia

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Introduction: Long-term patient response to non-nightly hypnotic use is not well described in the literature. This analysis evaluated efficacy trends of non-nightly dosing of zolpidem, over a 3-month period.
Methods: 199 patients (mean age 41 ± 12.8 years; 71% female) meeting the DSM-IV criteria for primary insomnia were randomized to either zolpidem 10 mg or placebo for a period of 12 weeks, in a double-blind, placebo-controlled clinical trial conducted at 9 centers. Sleep diaries were completed to assess the severity and frequency of sleep complaints and record medication use. Differences between the two groups were assessed for Sleep Latency (SL), Number of Awakenings (NOA), Wake After Sleep Onset (WASO), and Total Sleep Time (TST). Biweekly average values were for nights when patients took a pill (+Pill), nights when they abstained (-Pill), and for all nights (All). Analyses of treatment efficacy were conducted as serial ANOVAs with 3 mixed-model 2 × 7 ANOVAs run for each condition. Independent variables for each ANOVA were Group (2: zolpidem vs placebo) and Time (7: baseline and 6 biweekly time increments). Follow-up analyses to determine the stability of effects for the zolpidem groups used one-way ANOVAs (1 × 6).
Results: Zolpidem led to significant improvements in SL, NOA, WASO, and TST compared with placebo. Tolerance to medication was not evidenced. Three one-way ANOVAs for zolpidem groups (+Pill, -Pill, All) indicate that clinical gains were not reduced over time. SL showed a tendency to decrease (significant for -Pill, All; tended to be significant for +Pill, $P < 0.09$). Clinical gains for NOA and WASO were stable from weeks 1 and 2 to weeks 11 and 12. NOA and WASO did not significantly increase or decrease for +Pill or All; -Pill showed a tendency to decrease over study period for NOA ($P < 0.08$) and WASO. TST showed a tendency to increase over the study period (significant for -Pill, All; tended to be significant for +Pill, $P < 0.07$).
Conclusion: Observed clinical gains obtained with zolpidem did not diminish over the course of the 12-week study. The maintenance of clinical gains over the 3-month study interval suggests that, in the absence of dose escalation, habituation and tolerance do not occur with chronic intermittent use of zolpidem.

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Development And Validation Of The Glasgow Sleep Effort Scale

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Introduction: Good sleepers frequently report doing nothing to fall asleep. Whereas insomniacs often report deliberate attempts to control sleep. These observations support the hypothesis that good sleep is effortless, a natural default state supported by homeostasis and circadi-

an timing. They also support effort-based models of Paradoxical Intention (PI). PI is a probably efficacious insomnia treatment which directs insomniacs to remain passively awake at bedtime. It is thought to operate by reducing voluntary sleep effort, and thus may be suited to high effort insomniacs. Reaching this conclusion will require an acceptable, valid sleep effort scale. Here, we operationalise sleep effort, and report preliminary data for the Glasgow Sleep Effort Scale (GSES), a new self-report measure. Although previous scales have included effort items, no dedicated scale is published. This is despite routine use of PI within multi-component Cognitive Behaviour Therapy (CBT).
Methods: GSES items were derived using three processes: (1) an initial focus group (three sleep clinicians) delineating core effort themes; (2) an exhaustive content analysis of existing pre-sleep behaviour/cognition scales; (3) a confirmatory focus group delineating a working sleep effort model. Core behavioural (performance effort, sleep avoidance) and cognitive components of the model (anticipatory anxiety, night-time worry about sleep, general worry about sleep loss, dysfunctional beliefs regarding performance failure, control over sleep) were included in a draft GSES, given to 4 insomniacs, and 4 good sleepers. The scale readily distinguished insomniacs (mean = 8.5, SD 1.2) from good sleepers (mean = 0.75, SD 0.5). Discussions with two further insomniacs suggested acceptable face validity. The psychometric properties of a final 7 item GSES items were then examined. Insomniac participants were taken from General Practitioner referrals to a large insomnia trial reported elsewhere. Good sleepers were recruited via university email. The final sample comprised 65 insomniacs (mean age 49.6yrs, 60.1% female) and 110 good sleepers (mean age 33.9yrs, 48.6% female). Insomniacs met ICSD-R and DSM-IV criteria, and scored > 7 on the Pittsburgh Sleep Quality Index (PSQI). Good sleepers failed to meet criteria for sleep disturbance, reported good sleep, and scored < 5 on the PSQI. The GSES was completed at home.
Results: Mean total GSES score for insomniacs was 6.82, SD 3.6. Mean total GSES score for good sleepers was 1.29, SD 1.4. The GSES readily discriminated the groups ($t = -13.2$, $df = 173$, $p = 0.0001$). Distribution examination indicated limited overlap between highest scoring good sleepers and lowest scoring insomniacs. The relationship between GSES and PSQI scores was significant ($r = .76$, $p = 0.0001$). Cronbachs alpha was .77 using the insomniac group. Item-deletion alphas remained high, with little variation between values (mean = .75, range .74 - .76). Mean corrected item-total correlation was .66 (range .49 - .76). A score of 3 correctly identified 90.9% of good sleepers, and 80.0% of insomniacs.
Conclusion: The GSES is valid and reliable. It will identify insomniacs suited to CBT, or single component PI, provide a measure of clinical change and aid further research.

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Most Commonly Used Drugs to Treat Insomnia in 2002

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Introduction: From 1987 to 1996 dramatic changes in the pharmacological management of insomnia occurred, including: 1) the use of antidepressants (AD) increased 146%, 2) the use of drugs with an FDA indication for the treatment of insomnia (ID) fell 53.7%, and 3) the use of "other" drugs (e.g., antihistamines, barbiturates) fell 63.2%. At the end of that time period, AD were used as frequently as ID for the treatment of insomnia. Data from the Verispan, L.L.C. (Newtown, PA) Physician Drug and Diagnosis Audit (PDDA) for 2002 provided an updated estimate of the relative frequency for which various drugs were used to treat insomnia.
Methods: PDDA provides information regarding patient visits to office-based physicians and treatments associated with these visits. Approximately 3400 physicians, nationally representative for geographic region and for 29 medical specialties, report data for all patient visits within a 24-hr period, once per month. Data are then projected to represent the universe of office-based physicians in the United States. For this report treatment of insomnia was defined as a "drug occurrence" associated with a physician-specified desired action of "hypnotic", "promote/aid sleep" or "sedate night". Verispan provided the number of drug occurrences (and dose) associated with those desired actions for all ID, AD, anxiolytics, antihistamines, antipsychotics, and anticonvulsants, as well as all individual products, in the year 2002.
Results: AD accounted for 5.278 million (m) occurrences for the treatment of insomnia, as compared to 3.442m for ID, 0.822m for anxiolytics, 0.815m for antipsychotics, 0.552m for anticonvulsants, and 0.220m for antihistamines. The 16 most commonly identified individual drugs for the treatment of insomnia in 2002 were: trazodone (2.730m), zolpidem (2.074m), amitriptyline (0.774m), mirtazepine 0.662m), temazepam (0.558m), quetiapine (0.459m), zaleplon (0.405m), clonazepam (0.394m), hydroxyzine 0.293m), alprazolam (0.287m), lorazepam (0.277m), olanzapine (0.216m), flurazepam (0.205m), doxepin (0.199m), cyclobenzaprine (0.195m) and diphenhydramine (0.192m). The most common doses for the four leading insomnia medications were: trazodone 50mg = 53% of occurrences, 100mg=31%, 150mg=14%; zolpidem 10mg=70%, 5mg=29%; amitriptyline 10mg=29%, 25mg=38%, 50mg=19%, 100mg=8%; mirtazepine 15mg=41%, 30mg=55%.
Conclusion: The trends in the pharmacological treatment of insomnia identified from 1987 to 1996 appear to have continued. The present analysis suggests that in 2002 an AD was approximately 1.53 times more likely than an ID to be used for the treatment of insomnia by office-based physicians in the United States. Some of the factors likely to contribute to this practice are differences between ID and AD regarding: 1) recommended limitations on duration of use in the product label, 2) perceived abuse and dependence liability, and 3) DEA schedule status. Given this trend, more safety and efficacy data on AD used as hypnotics are clearly needed, and regulatory influences on this area of medical practice should be examined.

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Alcohol Used For Sleep and Increased Social Drinking

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Introduction: Population surveys have found that 15-35% of insomniacs report using alcohol as an aid to sleep. Laboratory studies have shown low dose ethanol initially improves the sleep of insomniacs, but within a week tolerance develops; when given an opportunity, insomniacs self-administer ethanol before sleep; and after six nights of a fixed dose, when given subsequent opportunity to take multiple doses, they increase the nightly dose. The critical issue is whether using alcohol for sleep then generalizes to social drinking resulting in increased social drinking. That is, in the general population is use of alcohol as a sleep aid associated with greater levels of social drinking.
Methods: A random-digit-dial, computer assisted, survey of a representative sample of adults, aged 18-65 yrs, was conducted. The sleep habits,

sleep problems, daytime sleepiness, health and psychiatric status, alcohol and drug use of 3,283 respondents in Metropolitan Detroit were assessed. In addition to assessing the quantity and frequency of social drinking, the survey inquired as to alcohol use to aid sleep in the past-year and the frequency of such use. The eligible household survey response rate was 68%. In the sample 6% reported daily alcohol consumption and 24% no alcohol consumption. To avoid biasing the results by heavy social drinking and possibly alcoholism, this report is based on the 70% of respondents who reported moderate alcohol consumption (n=2,282).
Results: Similar to previous surveys 16% (n=515) of the total sample (n=3,283) reported using alcohol as an aid to sleep. Among the moderate drinkers (n=2,282) 19% used alcohol to sleep. Respondents using alcohol for sleep reported a greater number of drinks per occasion (3.2+/-2.5 vs 2.7+/-2.1; p<.001) than those not using alcohol for sleep. Among individuals who used alcohol for sleep 73% reported continuous nightly durations of use for <1 wk, 12% 1-2 wks and 15% >2 wks and 82% reported a total of <30 nights of past year use, 10% 30-60 nights and 8% >60 nights. Those using alcohol to sleep for longer durations reported a greater number of drinks per occasion (p<.001) and those using alcohol for a greater number of nights the past year also reported a greater number of drinks per occasion (p<.001). Individuals who used alcohol for sleep rated their insomnia as more severe than those not using alcohol to sleep (p<.001). Among moderate drinkers 11% had insomnia as defined by DSM-IV consistent criteria. They reported consuming a greater number of drinks per drinking occasion (3.2+/-2.9 vs 2.7+/-2.2) than those not meeting insomnia criteria (p<.003). Of all meeting insomnia criteria 35% reported using alcohol for sleep and these individuals also showed a trend (p<.10) toward drinking a greater number of drinks per social occasion (3.8+/-3.1 vs 3.1+/-2.4).
Conclusion: Use of alcohol for sleep, as well as the extent of such use, is associated with greater social drinking. Severity and chronicity of insomnia further increases this association. These cross-sectional data need confirmation in prospective studies.

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Studio Morfeo 2: Sleep Dissatisfaction And Insomnia In A Primary Care Setting

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Introduction: Insomnia is the most common of all sleep disorders. Estimates from several countries indicate that about 30-48% of the adult population reports insomnia symptoms, but only 8-18% is dissatisfied with sleep quality or quantity. In the general population, sleep dissatisfaction is associated almost always to daytime consequences and these subjects are more likely to consult a physician about their sleep problem. The present investigation aims at exploring the prevalence and impact of sleep dissatisfaction in patients with insomnia symptoms in a primary care setting.
Methods: Data were collected from the Italian epidemiological survey called Studio Morfeo 2 carried out by 592 GPs. A screening questionnaire investigating insomnia symptoms and the current use of treatment was completed by a total of 26,919 patients aged ≥ 18 years, who referred to their GP for a clinical problem. Among the patients classified as insomniacs, 2,755 participants underwent a second investigation including demographic variables, socio-economic status, general medical situation, severity, duration and clinical characteristics of insomnia, daytime dysfunction, therapeutic management and sleep dissatisfaction. To investigate the relationship between sleep dissatisfaction and some of the population characteristics, a bivariate logistic analysis was carried out on the following covariates: age, gender, occupation, marital status, number of concomitant pathologies (≤1 vs > 1), insomnia symptoms (4 variables), presence of daytime complaints, number of diurnal disturbances (3 variables), duration of insomnia (≤ 12 months vs > 12 months), treatment for insomnia.
Results: Overall, 66% of patients with insomnia symptoms were dissatisfied with their sleep. Apart from the marital status, all the investigated variables were statistically significant. The highest odd ratio (CI 95%) was found for the presence of diurnal consequences (7.03; CI:5,69-8,68) Among diurnal disturbances, sleepiness was the most relevant complaint associated with sleep dissatisfaction (5.49; CI 4,61-6,52). All insomnia symptoms were highly significant with the greatest values expressed by non-restorative sleep (3.23; CI: 2,73-3,81) and by difficulty maintaing sleep (2.02; CI: 1,72-2,38). The presence of concomitant pathologies (0.84 CI: 0,72-0,99) and the duration of insomnia (0.58 CI: 0,48-0,69) had a slighter impact compared to employment (1.64 CI: 1,37-1,97), female gender (1.20 CI: 1,01-1,42) and young age (0.98 0,98-0,99). Treatment for insomnia (0.46 CI: 0,39-0,53) was significantly related to sleep dissatisfaction as the latter was more frequently reported in non-treated (73.7%) compared to treated patients (55.9%). Among the treated patients, sleep dissatisfaction was higher among non-responders (88.6%) than in responders (38.8%). Sleep dissatisfaction was found in 52.6% of the treated patients who used a single medication, a percentage that increased to 53.6% when 2 drugs were taken for insomnia, to 66.3% when 3 compounds were administered and to 81.8% with > 3 agents. Among the different drugs, hypnotics were the ones that less frequently were associated with sleep dissatisfaction (47.9%).
Conclusion: Sleep dissatisfaction is a reliable indicator of the sleep disturbance severity and management. In the Italian primary care population, sleep dissatisfaction was reported by 2/3 of insomniac patients. The risk of sleep dissatisfaction was higher in non-treated young, employed, female patients with insomnia symptoms associated with daytime complaints. The greater the amount of medication, the higher the risk of sleep dissatisfaction.

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Sleep-Consolidating Effects of Tiagabine in Patients With Primary Insomnia

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Introduction: GABAergic drugs have been shown to affect sleep. Tiagabine, a selective GABA reuptake inhibitor (SGRI), produces an increase in extracellular GABA by inhibiting GABA transport via GAT-1. Tiagabine has a tmax of 45 minutes in the fasting state and t1/2 of 7-9 hours in hepatically (CYP3A4) noninduced patients. In elderly volunteers, tiagabine has been shown to have sleep-consolidating effects. One aim of the present study was to determine the sleep-consolidating effects of tiagabine in nonelderly subjects with primary insomnia.
Methods: This was a cross-over (Latin-Square), double-blind, placebo-

controlled, dose-response study of tiagabine 4, 8, 12, 16 mg in subjects with primary insomnia. For each treatment period, study drug was administered for 2 consecutive nights (30 minutes before lights out) with a 5-12 day washout between treatment periods. Assessments included polysomnography and psychomotor performance (Digit Symbol Substitution Test, DSST) in the morning. Fifty-eight subjects met study criteria and were randomized. A qualitative treatment-by-period interaction was apparent (particularly for placebo treatment); thus efficacy data (reported as least-square means) are presented from period 1 only (n=11-12 per treatment group). Safety data are presented for all patients who received at least one dose of study drug (N=58).

Results: A reduction in wake after sleep onset (min) was observed, which was significant for the 8- and 12-mg doses (placebo=94.8, 4 mg=71.0, 8 mg=59.9 [p<0.04], 12 mg=61.4 [p<0.047], 16 mg=65.4). A dose-related decrease in number of awakenings was noted (placebo=11.0, 4 mg=12.3, 8 mg=9.2, 12 mg=9.3, 16 mg=8.9). Percent of sleep time in slow-wave sleep increased with dose (placebo=7.1%, 4 mg=10.8%, 8 mg=14.8%, 12 mg=25.6% [p<0.01], 16 mg=28.8% [p<0.01]), with dose-related reductions in all other stages of sleep (eg, Stage 1: placebo=11.2%, 4 mg=9.0%, 8 mg=8.0%, 12 mg=6.9%, 16 mg=12.9%; REM: placebo=18.8%, 4 mg=17.6%, 8 mg=17.6%, 12 mg=13.0% [p<0.05], 16 mg=10.1% [p=0.001]). The tolerability of tiagabine was dose-related. Residual effects, as measured objectively by the DSST, were present only for the 2 highest doses (DSST: placebo=65.4, 4 mg=64.1, 8 mg=64.4, 12 mg=61.1 [p=0.001], 16 mg=59.7 [p=0.001]). The most commonly reported adverse events were dizziness (placebo=0%, 4 mg=2%, 8 mg=0%, 12 mg=11%, 16 mg=21%), nausea (placebo=0%, 4 mg=0%, 8 mg=0%, 12 mg=7%, 16 mg=16%), and somnolence (placebo=2%, 4 mg=2%, 8 mg=0%, 12 mg=6%, 16 mg=9%). Patients who discontinued treatment due to adverse events received 1 of the 2 higher doses (n=2, 12 mg; n=5, 16 mg).

Conclusion: Tiagabine 8 mg and 12 mg were found to significantly consolidate sleep, as shown by a reduction in wake after sleep onset, and enhance "deeper" stages of sleep (ie, Stages 3 and 4). Doses up to 8 mg were well tolerated and not associated with objective residual effects. The clinical relevance of consolidating sleep is well documented; however, little is known about clinical correlates of making sleep "deeper." The utility of tiagabine 8 mg as a potential sleep-enhancing agent warrants further research.

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Efficacy of Eszopiclone in the Treatment of Sleep Maintenance Insomnia: A Subset Analysis by Baseline Wake After Sleep Onset (WASO)

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Introduction: The most common complaint among patients with insomnia is difficulty staying asleep. As a result, efficacy in maintaining sleep (sleep maintenance) is an important attribute of a medication used to treat insomnia. A 6-month placebo-controlled study demonstrated that eszopiclone has statistically significant efficacy in all aspects of sleep including sleep onset, maintenance, quality, and self-reported daytime function. This study provided evidence for sustained sleep maintenance efficacy in the form of significantly greater improvement in WASO vs. placebo throughout the study. Inclusion criteria for the patients in this study included decreased total sleep time and/or sleep onset latency. We now report analyses carried out in subgroups defined by baseline WASO in order to evaluate whether eszopiclone is effective in those with substantial sleep maintenance problems and to estimate the effects of eszopiclone in patients selected for difficulties in staying asleep.

Methods: Patients meeting DSM-IV criteria for primary insomnia who reported a total sleep time of less than 6.5 hours and/or a sleep onset latency of more than 30 minutes were entered into a 6-month, randomized, double-blind, placebo-controlled, multi-center study of eszopiclone 3mg (n=593 eszopiclone; n=195 placebo; male and female 21-64 years of age). Among the outcome measures entered weekly by telephone via an interactive voice response system, this analysis focused on self-reported WASO. For analysis, patients were grouped by baseline WASO into Low-WASO (<60 minutes; n=336) and High-WASO (≥ 60 minutes; n=340). WASO in those receiving eszopiclone and placebo in the Low-WASO groups was compared to that in the High-WASO groups. We also carried out an analysis of all patients who had greater than 30 minutes of WASO at baseline as this is a common threshold for clinical significance and has been the entry criterion for studies assessing sleep maintenance.

Results: Over each of the 6 months of the study and for the 6 months overall, statistically significant differences from placebo were noted in both groups. In the Low-WASO group, treatment with eszopiclone resulted in a median WASO of 19 minutes whereas the median WASO with placebo was 30 minutes (p=0.0035). In the High-WASO group, the median WASO following treatment with eszopiclone was 39 minutes vs. 60 minutes for placebo (p=0.0055). Patients who had >30 minutes of WASO at baseline had greater reductions in WASO than placebo (24-41%).

Conclusion: Eszopiclone 3mg was effective at reducing WASO in patients with both high and low baseline WASO and maintained this effect over the study period. This indicates that eszopiclone may be effective in the treatment of sleep maintenance insomnia.

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Polysomnographic and Patient-Reported Evaluation of the Efficacy and Safety of Eszopiclone in Elderly Subjects with Chronic Insomnia

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Introduction: Insomnia occurs at an increased frequency in the elderly compared with non-elderly adults; about 50% of the elderly complain of difficulty staying asleep or falling asleep as compared with about 30% of the general population. Chronic insomnia also produces decreased daytime quality of life (QoL). Some patients with insomnia may nap in the daytime to compensate for poor quality or reduced amounts of sleep. Eszopiclone is a novel, non-benzodiazepine cyclopyrrolone agent under development to treat insomnia and has been shown to rapidly induce and maintain sleep. This study evaluated the efficacy and safety of eszopiclone in elderly patients with chronic insomnia.

Methods: In this randomized, double-blind, placebo-controlled study, 264 patients 65-85 years of age with a DSM-IV diagnosis of primary insomnia received eszopiclone 2mg (n=136) or placebo (PBO, n=128) nightly for 2 weeks. Efficacy endpoints assessed via polysomnography (PSG) included latency to persistent sleep (LPS), sleep efficiency (SE), WASO, and number of awakenings. Patient-reported data were collected via an interactive voice response system in the morning (to assess sleep parameters) and in the evening (to assess daytime function) and included sleep latency (SL), sleep maintenance (wake time after sleep onset [WASO] and awakenings), total sleep time (TST), quality and depth of sleep, and morning sleepiness. Next day functioning parameters were assessed each evening. QoL was assessed using the Insomnia

Severity Index and SF-36 questionnaires.
Results: Compared with placebo, eszopiclone 2mg significantly reduced objective LPS ($p<0.0001$) and WASO ($p<0.05$) over the treatment period. SE was also significantly increased over the treatment period ($p<0.04$), and PSG awakenings were reduced ($p=0.16$). Patient-reported SL ($p<0.0001$ vs. placebo), WASO ($p=0.0019$) and TST ($p\leq0.0001$) were also significantly decreased, and awakenings were reduced ($p=0.051$). Eszopiclone reduced the cumulative number of naps ($p=0.03$) and duration of naps ($p=0.07$) among patients who napped, and reduced morning sleepiness ($p=0.07$, overall). Eszopiclone produced improvement in the Insomnia Severity Index total score ($p=0.0001$) and quality of sleep ($p=0.0002$), and improvements in the SF-36 domains of physical functioning ($p=0.045$) and vitality ($p=0.056$). There was no rebound insomnia after treatment withdrawal, and eszopiclone was well tolerated. The most common adverse event was unpleasant taste.
Conclusion: In elderly patients with chronic insomnia, eszopiclone 2mg produced consistent, statistically significant improvement in both PSG- and patient-reported measures of sleep, including onset and maintenance. There was less daytime sleep (napping) and improvements were observed in some of the QoL domains as measured by validated instruments. These findings are unique among studies of insomnia in the elderly and may have important implications for the treatment of insomnia in elderly patients.

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Eszopiclone Efficacy and Daytime Functioning in Non-Elderly and Elderly Patients with Chronic Insomnia

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Introduction: Insomnia affects about 36% of adults, and prevalence increases with age. DSM-IV defines primary insomnia as difficulty initiating or maintaining sleep or of non-restorative sleep accompanied by next day impairment, yet most studies of hypnotics do not include measures of next day function. Eszopiclone is a non-benzodiazepine compound previously shown in both elderly and non-elderly patients to rapidly induce and maintain sleep. Data from 3 randomized, double-blind, placebo-controlled studies of eszopiclone in patients with a DSM-IV diagnosis of primary insomnia are compared to determine if eszopiclone demonstrates efficacy and daytime effects that are consistent across studies and patients.
Methods: Study 1 was a 2-week study of eszopiclone 2mg in elderly patients (age 65-85 years; n=160). Study 2 was a 6-week efficacy study of eszopiclone 3mg (age 21-64; n=204), and Study 3 was a 6-month study of eszopiclone 3mg (age 21-64; n=788). All treatments were administered nightly in a double-blind manner, and each study captured patient reports of efficacy collected using an interactive voice response system. Each study evaluated sleep onset, sleep duration, and sleep maintenance (wake after sleep onset-WASO), and various measures of daytime function.
Results: Across all 3 studies, in both elderly and non-elderly patients, eszopiclone significantly improved patient reports of sleep latency, WASO, and TST compared with placebo. Sleep latency and WASO were significantly decreased (sleep latency, $p<0.01$; WASO, $p<0.05$) and total sleep time was significantly increased ($p<0.01$). In each study, eszopiclone patients reported improvements in measures of daytime function. In Study 1, after 2-weeks of treatment, improvements were noted in daytime alertness ($p<0.05$), morning sleepiness ($p=0.055$), sense of well-being ($p<0.05$), and daytime ability to function ($p=0.058$). In Study 2, after 6 weeks, eszopiclone treatment resulted in improvements in daytime alertness ($p=0.07$) and ability to function ($p=0.06$) compared with placebo. In Study 3, at every month over 6 months of treatment, eszopiclone significantly improved daytime alertness, ability to function (captured as ability to concentrate), and sense of physical well being (all p-values <0.002).
Conclusion: These data indicate that eszopiclone provides consistent improvements in patient-reported measures of sleep in elderly and non-elderly patients with chronic insomnia. Notably, consistent improvements in patient ratings of daytime functioning were also reported, indicating that eszopiclone may demonstrate efficacy in improving all four components of the DSM-IV diagnosis of primary insomnia.

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Non-Nightly Administration of Zolpidem for Treatment of Primary Insomnia Does Not Lead to Dose Escalation

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Introduction: It has not been well-established whether those who take hypnotics on a non-nightly basis experience tolerance to the therapeutic effects over time or are at increased risk for non-therapeutic medication use. The focus of this analysis was to determine whether these phenomena occur by assessing if intermittent long-term zolpidem usage was associated with an escalation in the number of nights that subjects chose to take medication over time.
Methods: 199 patients (mean age 41 ± 12.8 years; 71% female) meeting the DSM-IV criteria for primary insomnia were randomized to either zolpidem 10 mg or placebo for a period of 12 weeks, in a double-blind, placebo-controlled clinical trial conducted at 9 centers. Sleep diaries were completed to assess the severity and frequency of sleep complaints and record medication use. Participants were instructed to take at least 3 but no more than 5 pills per week. Unused medication was returned to study site at each visit for verification purposes. Analysis was conducted using a 2 × 6 ANOVA. Variables for each ANOVA were the number of pills taken per week by Group (zolpidem vs placebo) and Time (6 biweekly time increments). Point-to-point between-group comparisons were accomplished with Duncan t-tests.
Results: The interaction of Group by Time was not significant (Group = .0005, Time = 0.0319; Group × Time = NS), and no trend was evident ($P > 0.15$). The main effect for Group indicated that the placebo group averaged one pill less per 2-week interval. The main effect for Time suggests both groups exhibited a trend toward an increase in number of pills per week. The failure to resolve the Group by Time interaction suggests the tendency to increase weekly pill intake over time did not occur for one group more than the other.
Conclusion: There was no evidence that patients using zolpidem escalated their medication intake, as compared with the placebo group. Participants using zolpidem voluntarily limited usage to 80% of available medication. Increases in usage represented only 20% of the possible increase and this trend did not differ from that of the patients taking

placebos.

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Objective and Subjective Insomnia: Predictors of Sleep State Misperception

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Introduction: Several studies have shown that many patients who meet the DSM-IV-TR criteria for primary insomnia will not have their complaints confirmed by polysomnography. These findings have led to a classification of subjective insomnia or sleep state misperception. Sleep state misperception is defined as a condition that involves a complaint of insomnia in combination with a normal sleep study that shows no difficulty initiating or maintaining sleep. The main treatments provided for patients complaining of insomnia are hypnotic medications that have been shown to be effective in treating both the objective and subjective aspects of insomnia, but do have side effects, and behavioral modification treatments that are effective only in treating the subjective symptoms. Therefore those patients with sleep state misperception can be effectively treated with behavioral treatment and avoid unnecessary exposure to the side effects of the pharmaceutical interventions. Unfortunately it is too costly to perform sleep studies on all patients who complain to their physicians of insomnia. The purpose of this study was to determine what demographic factors best predict whether or not a patient has objective insomnia or sleep state misperception. Identifying reliable predictors of sleep state misperception may allow physicians to prescribe appropriate treatment to these patients.
Methods: Demographic data were collected from 63 participants who met the DSM-IV-TR criteria for primary insomnia. These participants were separated into two groups: those with objective insomnia (n=22) and those with subjective insomnia or sleep state misperception (n=41) as determined by polysomnography. The following demographic data were collected from these patients: age, gender, height, weight, number of medications used, and number of items in medical history. These factors will then be placed in a logistic regression to determine the best predictor(s) for sleep state misperception.
Results: Using the backward elimination technique the logistic regression identified age as the only demographic factor found to predict diagnosis at the p = .10 level: age (OR = 1.05, 95%CI = 0.998 to 1.106, p= .057). 65.1% of the respondents had sleep state misconception that would constitute this study's baseline group prediction rate. The results of the logistic regression model improved the correct percentage of classification to 76.2%. More specifically, sleep state misperception was correctly classified in 39 of 41 cases (95.1%), and primary insomnia was correctly classified in 13 of 22 cases (59.1%).
Conclusion: The results of this study show that a subject's age is an important factor in determining appropriate treatment for patients who complain of insomnia. This logistic regression model shows that the younger a patient is, the more likely they are to fall into the subjective group of insomnia sufferers. Future research should look to identify other significant predictors using larger sample sizes and more predictor variables (e.g. Beck Inventory, prior use of hypnotics, etc.).

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Treatment of Primary Insomnia For Five Weeks With Indiplon-IR

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Introduction: : Indiplon, a GABA potentiator with selectivity for receptors with the alpha1 sub-unit, is being evaluated for the treatment of both transient and chronic insomnia. The Indiplon-IR formulation is rapidly absorbed and has an elimination half-life of 1.0 to 1.5 hours. The current multicenter, placebo-controlled study was designed to evaluate the efficacy, tolerability, and safety of indiplon-IR for the treatment of chronic insomnia when administered for 35 consecutive days.
Methods: One hundred ninety-four adult patients were randomized and received double-blind study drug. (66% female; mean age, 40.2+11.8 years). All met DSM-IV criteria for primary insomnia of at least 3 months duration, and reported a usual latency to sleep onset (LSO) >30 min, and usual total sleep time (TST) <6.5 h). PSG documented a latency to persistent sleep (LPS) >25 min on 2/3 screening nights. Following PSG screening and a placebo lead-in period; eligible patients were randomized to 5 weeks of double-blind treatment with either 10mg or 20mg doses of indiplon-IR, or placebo (PBO). PSGs were performed on nights 1 and 2 (week 1), 15 and 16 (week 3), 29 and 30 (week 5) of study drug administration, as well as nights 1 and 2 of single-blind drug discontinuation. Subjective data were obtained with a morning sleep questionnaire. Next day residual effects were evaluated using the Digit Symbol Substitution Test (DSST), Symbol Copy Test (SCT), and a Visual Analog Scale rating of sleepiness (VAS). Discontinuation effects were evaluated using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ).
Results: Indiplon-IR significantly reduced LPS at all time points for both doses. During week 1, LPS for the 10mg, 20mg, and PBO groups were 27.7 min ($p<0.01$ vs PBO), 27.1 min ($p<0.05$ vs PBO), and 36.9 min, respectively. LPS at 3 weeks and 5 weeks were:10mg (30.4 min and 29.2 min, respectively; $p<0.01$ vs. PBO); 20mg (28.7 min and 24.8 min; $p<0.05$ vs. PBO); and PBO (40.0 min and 40.1 min). TST was greater than PBO only during week 1 for the 10mg group ($p<.02$). Subjective ratings of LSO were significantly reduced for both 10mg (49.8 min; $p<0.0001$) and 20mg (44.4 min; $p<0.003$) compared to PBO (72.5 min) during week 1. LSO for both dose groups was also reduced vs PBO during week 5 ($p<.02$ for both), and there was a trend for both groups during week 3 (due to a transient improvement in PBO group). Sleep quality was better with both Indiplon-IR doses than PBO during week 1 only ($p<0.03$). There were no differences between either dose of indiplon-IR and PBO on any measure of residual effects. No serious adverse events occurred. Reported adverse events were equally common in the PBO and 10mg groups, and were infrequent and related to the pharmacological activity of the drug in the 20mg group. No PSG or subjective evidence of rebound insomnia was noted. BWSQ scores did not differ among groups at discontinuation.
Conclusion: In patients with primary insomnia, the 10mg and 20mg doses of indiplon-IR significantly reduced LPS during the 5 weeks of study with comparable findings for LSO. Indiplon-IR 10mg was well-tolerated, as was 20mg by the large majority of patients, with no unexpected adverse events, no evidence of next day residual effect, and no evidence of withdrawal or rebound upon abrupt discontinuation.

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Residual Effects Of Middle Of The Night Dosing: A Placebo-Controlled Crossover Study Of Indiplon-Ir, Zolpidem, And Zopiclone In Healthy Volunteers

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Introduction: A common complaint in chronic insomnia patients is middle of the night awakening with difficulty returning to sleep. Such sleep disruptions are often managed by middle of the night (MOTN) dosing with hypnotics. Previous studies indicate that zolpidem and zopiclone may impair next-day cognitive, memory and psychomotor performance after MOTN-dosing. Agents with shorter half lives may represent more appropriate candidates for MOTN dosing. Indiplon, a GABA potentiator with selectivity for receptors with the alpha1 sub-unit and a short elimination half life, is a new investigational therapy for insomnia. The current study was designed to assess the next day residual effects of MOTN-dosing with the immediate-release (IR) formulation of indiplon in healthy adults.
Methods: This was a single-center, randomized, double-blind, 5-way crossover study in which indiplon-IR 10mg and 20mg doses, zolpidem 10mg, and zopiclone 7.5mg were compared to placebo in healthy volunteers, aged 18-45 years (N=35; 43% female; mean age, 32 years). Crossover treatment periods were each separated by a 72-96 hour drug-free interval. Subjects received a single dose of study drug in the middle of the night, four hours after bedtime. At 4 hours post-dose, the subjects were awakened and pharmacodynamic assessments were conducted at both 4 and 6 hours after study drug administration. Next day residual effects were evaluated by the Digit Symbol Substitution Test (DSST), Symbol Copying Test (SCT), and a 100-mm Visual Analog Scale of sleepiness (VAS). Reports of adverse events were also collected.
Results: Compared to placebo, there were no statistically significant changes from pre-dose baseline in the VAS-sleepiness ratings at either 4 hours or 6 hours post-dose with indiplon-IR 10mg or 20mg. In contrast, zopiclone showed a significant increase relative to placebo in sleepiness at both 4 hours ($p<0.0001$) and at 6 hours ($p=0.0002$). Similarly, zolpidem showed a significant increase in sleepiness at 4 hours post-dose relative to placebo ($p=0.042$), but not at 6 hours. No statistically significant changes were noted from pre-dose to 4 hours or 6 hours post-dose on indiplon-IR, zolpidem, or zopiclone on either the DSST or SCT. The incidence of any treatment-emergent adverse events was comparable for placebo (8.6%), indiplon-IR 10mg (5.9%) and 20mg (11.8%) and zolpidem (11.4%). In contrast, the incidence of adverse events for zopiclone was 29%.
Conclusion: The results of this study indicate that middle of the night treatment with 10mg and 20mg doses of indiplon-IR does not result in next-day residual effects. In contrast, middle of the night treatment with zolpidem and zopiclone are associated with significant residual sedation. The data suggest that indiplon may have a suitable profile for middle of the night administration.

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WITHDRAWN

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Twelve Months of Nightly Eszopiclone Treatment in Patients with Chronic Insomnia: Assessment of Long-Term Efficacy and Safety

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Introduction: Although insomnia agents may be used long-term to treat chronic insomnia, long-term efficacy has not been demonstrated. We previously reported that eszopiclone led to significant and sustained improvement in sleep onset, maintenance, and quality as well as self-reports of daytime function vs placebo in the 6 month, double-blind portion of this 12-month study. Here, we present the results of the 6-month open-label extension phase, designed to evaluate continued efficacy and safety.
Methods: Males and females between 21 and 64 years of age who reported sleeping no more than 6.5 hours per night and/or taking more than 30 minutes each night to fall asleep were included. Endpoints were patient reported, captured weekly using an interactive voice response system and included sleep parameters (sleep latency, total sleep time, WASO, number of awakenings, number of nights awakened, quality of sleep) and daytime function (daytime alertness, physical well-being, and daytime ability to function [concentrate]). Safety and compliance assessments were carried out at monthly clinic visits.
Results: In the double-blind portion of the study, relative to placebo, eszopiclone 3mg produced significant, sustained improvements in every efficacy measure, including all measures of sleep induction, maintenance, and quality at every time interval during the 6-month treatment period. Following the 6-month, double-blind portion, 471 patients (111 placebo, 360 eszopiclone) entered the extension phase and received open-label eszopiclone 3mg nightly at bedtime. Patients previously treated with placebo reported rapid and significant ($p<0.05$) improvements in sleep and daytime functioning. Their data were not significantly different from those of patients who received eszopiclone in the double-blind phase. These improvements in reports of sleep and daytime function were sustained for the entire 6-month extension period. At the end of the extension phase, 86 of 111 patients who were originally randomized to receive placebo had received eszopiclone 3mg for 6 months (6 months double-blind placebo + 6 months open-label eszopiclone), and 296 of 360 patients had received eszopiclone for 12 months (6 months double-blind eszopiclone + 6 month extension phase). Administration of eszopiclone 3mg to patients with chronic insomnia for up to 12 months was well tolerated. There was no evidence of development of tolerance and no significant adverse events commonly associated with withdrawal upon discontinuation. There was no evidence of drug-related safety issues in vital signs, laboratory or ECG measures, or in physical examination findings during the double-blind or open-label periods.
Conclusion: Eszopiclone provided and maintained sustained improvement in patient-reported sleep and daytime functioning in patients with chronic insomnia over 12-months of therapy, was well tolerated, and did not demonstrate evidence of tolerance or withdrawal.

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Assessment Of Respiratory Effects Of Indiplon-Mr In A Co2 Challenge Model

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Introduction: Traditional benzodiazepine hypnotics may have the adverse effect of respiratory depression in at-risk populations (eg, COPD, sleep apnea). These adverse respiratory effects are both centrally and peripherally mediated. Indiplon, a GABA potentiator with selectivity for receptors with the alpha1 sub-unit, is a new investigational therapy for insomnia. The modified release (MR) formulation of indiplon has demonstrated efficacy in inducing and maintaining sleep, without next day residual effects. The goal of the current study was to evaluate the potential for respiratory depressant effects of a 30mg daytime dose of indiplon-MR in a CO2 challenge model. Codeine 60mg was used as an active control.
Methods: 12 healthy male volunteer subjects were enrolled (mean age, 32 years). Subjects were randomized, in a double-blind crossover design, to treatment with a single dose of indiplon-MR 30mg, codeine sulfate 60mg, or placebo. Each treatment was separated by a washout period of at least 72 hours. Ventilatory and mouth occlusion pressure responses to CO2 challenge, and arterial oxygen saturation (SaO2), were measured 1 hour before and at 1, 2, 4, 6, 8 hours after dosing.
Results: Indiplon had no statistically or clinically significant effects on respiratory function compared with placebo as assessed by minute ventilation (Ve) in response to CO2 challenge, mouth occlusion pressure in response to CO2 challenge, resting mean inspiratory flow at pre-CO2 challenge, resting end tidal PCO2 of expired air at pre-CO2 challenge, and SaO2. Following treatment with codeine sulfate 60mg, respiratory suppression on Ve was observed in response to CO2 challenge at all post-dose timepoints, with the most notable reductions from mean predose values observed at 1 -23%) hour and 6 hours (-35%) post-dose. Indiplon was well tolerated, with no serious adverse events or discontinuations due to adverse events reported during this study. There were no clinically significant changes in clinical laboratory tests, ECG, vital sign measurements, or physical examination findings.
Conclusion: The 30mg dose of indiplon-MR was well-tolerated in this sample of healthy volunteers. Indiplon-MR had no clinically significant effect on respiratory drive following CO2 challenge.

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A Pooled Analysis of Eszopiclone in the Treatment of Insomnia in the Elderly

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Introduction: The prevalence of insomnia, which affects about 36% of adults, increases with age. Primary insomnia is defined (DSM-IV) as difficulty initiating or maintaining sleep or of non-restorative sleep accompanied by next day impairment, yet most studies of hypnotics do not include measures of next day functioning. Eszopiclone is a novel, non-benzodiazepine cyclopyrrolone agent under development to rapidly induce and maintain sleep in patients with insomnia. Eszopiclone has demonstrated improvements in both sleep and daytime functioning in a large (n=788) 6-month study in adults with chronic insomnia. Two studies have been conducted in the elderly, but the sample size of each was 25% of that of the 6-month study. In order to determine whether similar improvements in both sleep and daytime functioning occurred in a larger sample, data from the elderly studies was combined (pooled); the results of these analyses are presented here.
Methods: Both studies were randomized, double-blind, placebo-controlled evaluations in elderly patients (ages 64-85) with chronic insomnia. Patients received nightly treatment with eszopiclone 2mg (n=215) or placebo (n=207) for 2 weeks. Patient-reported endpoints assessed in both trials were measures of sleep and next day sleepiness and daytime functioning. Data were collected twice each day using an interactive voice response system.
Results: At Week 1, Week 2, and over the treatment period, eszopiclone significantly decreased median sleep latency ($p<0.0001$), wake time after sleep onset ($p\leq0.01$), total sleep time ($p<0.0001$), sleep quality ($p\leq0.01$), and sleep depth ($p\leq0.007$) vs. placebo. Over the double-blind period, median sleep latency was 53 minutes for placebo, compared with 30 minutes for eszopiclone ($p<0.0001$), while median total sleep time was 335 minutes and 385 minutes, respectively ($p<0.0001$). The number of awakenings was also reduced at Week 1 ($p<0.002$), Week 2 ($p=0.06$), and over the double-blind period ($p<0.02$). In addition, the cumulative number of naps over the 2-week period was significantly reduced ($p=0.002$) among patients who napped, as was the duration of naps ($p<0.001$). Improvements in sleep were accompanied by improvements in next day functioning. Over the double-blind period, there were significant improvements in morning sleepiness ($p=0.01$) and daytime alertness ($p=0.02$), and improvements in ability to function ($p=0.07$) and sense of well-being ($p=0.11$). Treatment was well-tolerated, and the most common adverse events were headache (approximately 14% in both groups), unpleasant taste (12% in the eszopiclone group), and dry mouth (7%, eszopiclone).
Conclusion: Two weeks of nightly treatment with eszopiclone 2mg was well tolerated and improved patient reported measures of sleep onset, sleep maintenance, sleep quality, and next day functioning in elderly patients with chronic insomnia, all of which are components of the DSM-IV diagnosis of primary insomnia.

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Safety Of Indiplon-MR In Patients With Mild-To-Moderate COPD

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Introduction: Chronic Obstructive Pulmonary Disease (COPD) affects approximately 20% of adults, and is associated with a rate of comorbid insomnia that exceeds 50%. Benzodiazepine hypnotics continue to be widely used to treat insomnia in COPD, despite evidence of adverse respiratory effects in a subset of patients. Indiplon, a GABA potentiator with selectivity for receptors with the alpha1 sub-unit, is a new investigational therapy for insomnia. Modified release (MR) indiplon has demonstrated significant efficacy in inducing and maintaining sleep, without next-day residual effects as compared to placebo. The goal of the current study was to evaluate the respiratory depressant effects, and overall safety and tolerability, of a 20 mg dose of indiplon-MR in subjects with mild to moderate COPD.
Methods: 18 subjects were enrolled (N=10 female; mean age, 53 yrs); 78% with moderate COPD (defined as an FEV1 30-80% of predicted, and an FEV1/FVC ratio<70%) and 22% with mild COPD (FEV1

>80%). After a single-blind placebo lead-in to establish a polysomnography (PSG) baseline, subjects were randomized double blind to one night of treatment with indiplon-MR 20mg and placebo. Study dosing occurred on 2 consecutive nights. Primary outcomes consisted of arterial oxygen saturation (SaO2) by pulse oximetry, and the respiratory disturbance index (RDI), calculated as the total number of apnea/hypopnea events divided by total sleep time. Sleep quality was assessed using a 7-point subjective sleep quality morning questionnaire.
Results: Mean whole night SaO2 was similar for indiplon-MR (93.6 + 0.4%) vs. placebo (93.4 + 0.4%). No difference between indiplon-MR and placebo was observed in mean SaO2 during REM (93.0% vs. 92.8%) and non-REM sleep (93.0% vs. 92.9%). Mean RDI was also similar for indiplon-MR (2.7 + 0.7) vs. placebo (3.2 + 0.7). Sleep quality was subjectively rated as "very good" or "excellent" by 50% of subjects on indiplon-MR vs. 17% of subjects on placebo. Indiplon-MR was found to be safe, with no treatment-emergent changes in ECG or laboratory values.
Conclusion: In this single-dose study of patients with mild-to-moderate COPD, indiplon-MR was well-tolerated, and had no clinically significant effects on respiratory function as assessed by SaO2 and RDI. Indiplon-MR was also associated with improved sleep quality relative to placebo.

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Efficacy Of Indiplon In Inducing And Maintaining Sleep In Patients With Chronic Sleep Maintenance Insomnia

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Introduction: Difficulties with sleep maintenance are the most frequent clinical presentation of chronic insomnia in adults over the age of 40. Nonetheless, studies specifically designed to recruit and evaluate treatment efficacy in this patient population are less common. Since difficulty with initiating sleep is a frequent secondary complaint, the ideal sleep maintenance medicine will demonstrate rapid absorption and onset of activity, maintain therapeutic blood levels throughout the night and then be rapidly cleared from plasma to avoid next day residual effects. Indiplon is a GABA potentiator with selectivity for receptors with the alpha-1 sub-unit. The modified release (MR) formulation, indiplon-MR, has been developed with respect to these criteria. The current study was designed to evaluate the efficacy and safety of this novel indiplon-MR formulation for the treatment of sleep maintenance insomnia.
Methods: Adult outpatients who met DSM-IV criteria for primary insomnia for >3 months, with usual total sleep time <6.5 hours and wakefulness after initial sleep onset >0.75 hours and, completed a 2-week placebo lead-in, and then were randomized to 2 weeks of double-blind indiplon-MR 30mg or placebo (N=211; 68% female; mean age, 48 years). The primary endpoint was subjectively rated total sleep time (sTST); additional endpoints included latency to sleep onset (LSO), subjective wake time after sleep onset (sWASO), subjective number of awakenings after sleep onset (sNAASO), sleep quality (SQ) and patient global impressions of study drug on a 5-item scale (PGI). Investigators provided a global rating of severity and change on 7-point improvement scales.
Results: Indiplon-MR 30mg significantly increased sTST relative to placebo both at week 1 (375 min vs. 328 min, p<0.0001) and at week 2 (367 min vs. 336 min, p=0.0013). In addition, indiplon-MR significantly reduced sWASO relative to placebo at both week 1 (54 min vs. 79 min, p<0.0001) and week 2 (51 min vs. 73 min, p=0.0003). sNAASO was also significantly reduced at both weeks. Initiating sleep, as measured by LSO, was also significantly improved on indiplon-MR relative to placebo both at week 1 (30 min vs. 37 min, p=0.0084) and at week 2 (27 min vs. 33 min, p=0.0131). Subjective ratings of sleep quality were significantly improved on indiplon-MR (p<0.0001) at week 1 and week 2. PGI ratings were significantly improved on all 5 items (overall effect on sleep, effect on sleep quality, strength of medicine, time to fall asleep and duration of sleep) for indiplon-MR relative to placebo (p<0.002 for all comparisons at both week 1 and week2). Investigator global ratings demonstrated significant improvements in severity and change scores for indiplon-MR relative to placebo (p<0.0001 for both comparisons). Indiplon-MR was well-tolerated, with no serious adverse events reported.
Conclusion: Indiplon-MR 30mg was well-tolerated in this study of patients with chronic sleep maintenance insomnia, demonstrating significant efficacy in inducing and maintaining sleep, with significant improvements in sleep quality as well as in patient and investigator global ratings of efficacy.

This research was supported by Neurocrine Biosciences, Inc.

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Trajectory Analysis of Treatment Response During a Six-month Study of Nightly Eszopiclone in Patients with Chronic Insomnia

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Introduction: Little is known about the long-term efficacy of benzodiazepine receptor agonists for treating insomnia. Eszopiclone demonstrated statistically significant improvements in mean and median measures of self-reported sleep and daytime function versus placebo throughout a six-month double-blind treatment period. These analyses do not indicate whether specific patients may have had different patterns of treatment response. For instance, some may have shown progressive improvement over time, whereas others may have developed tolerance. The aim of this study was to determine whether distinct patterns of treatment response could be identified among eszopiclone or placebo-treated patients in the six-month study.
Methods: Subjects included 788 men and women 21-64 years of age who reported insomnia (sleep duration ≤6.5 hours and/or sleep latency >30 minutes). Treatment consisted of randomized, double-blind eszopiclone 3mg or placebo, taken nightly for six consecutive months. Weekly self-report sleep data were collected using an interactive voice recording system. Endpoints of sleep latency, total sleep time, and wake after sleep onset were examined using trajectory analysis, a statistical technique that fits semi-parametric mixture models to identify different longitudinal data trajectories within a sample. In this case, we analyzed weekly sleep data during treatment using the SAS TRAJ procedure, in order to identify different patterns of treatment response. We empirically tested models with 2-5 trajectories for each treatment. The SAS TRAJ procedure calculates the probability of each subject belonging to each trajectory, and assigns each subject to the most likely trajectory. Linear and quadratic mixture models were tested, using separate models for eszopiclone and placebo groups.
Results: We first tested linear mixture models for the three sleep endpoints in the eszopiclone group. For each endpoint, trajectories of treatment response subgroups had similar slopes, whether we specified 2, 3, 4, or 5 subgroups, and whether or not we added a quadratic term. The subgroups differed only in terms of mean symptom levels, but not in their actual time course. Descriptively, each of the subgroups showed a

rapid treatment response followed by a stable course or slight improvement over the subsequent six months. We then tested similar models for the placebo group. Once again, trajectories of treatment response for each sleep endpoint had similar slopes regardless of whether we specified 2-5 groups, or whether a quadratic term was added. The subgroups again differed only in terms of mean symptom level. Descriptively, each placebo subgroup showed a stable course or slight improvement over the six months of treatment.
Conclusion: We did not find distinct treatment response trajectories in insomnia patients treated with eszopiclone or placebo for six consecutive months. These results stand in stark contrast to similar analyses in other disorders, e.g., depression treatment, where 2-4 distinct treatment response profiles are readily identified. The results provide further evidence that six months of nightly eszopiclone treatment is associated with rapid and sustained response and no evidence of tolerance, even among different patient subgroups.

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New Approach to Insomnia Measurement: Sample the Experience During the Night
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Introduction: Examining the subjective details of insomnia sufferers' bad nights has received some attention in recent years. This research has collected and coded the experiential details of difficulty sleeping. These investigators seek alternative ways to describe insomnia. The present study monitored the insomnia experience during the night, while the difficulty with sleep was unfolding.
Methods: The monitoring is done with a SOMTRAK ™ audio recording device that is programmed to intermittently sound a soft signal tone, then turn on a tape recorder that collects a 20–second recording of sounds in the bedroom. The recording cycles that consist of a signal tone, then an audio recording, occur once every 10 minutes (i.e., audio samples are collected 6 times per hour). In the present study, participants are trained to briefly summarize aloud what is being experienced each time a signal tone is heard. The soft tones are only heard if the person is awake; in other words, the tones are quiet enough they do not disturb sleep. Previous research has shown they are not intrusive. Four poor sleeper participants have been tested with this assessment approach, for a total of 45 nights. We plan to complete testing of 15 participants prior to the APSS meeting. We train research participants to mentally scan what they experience during each awakening and train them to quickly answer 5 probing questions about the contents of subjective experience. The questions have been shaped by popular hypotheses about insomnia. The questions are to be answered aloud each time the person hears the recording device sound the barely audible tone cue. The five questions are brief and use code words for common experiences; they have brief, 2 or 3 word answers. The questions are: (1) "Feel sleepy or don't feel sleepy?" (2) "Reviewing and analyzing or mind fairly quiet?" (3) "Worrying or not worrying?" (4) "Body relaxed or body not relaxed?" (5) "Mood O.K. or negative mood?" The last four questions tap into common experiences thought to be basic elements of chronic insomnia - cognitive over–activity, worry, physiological over–arousal and negative affect.
Results: Eighteen long awakenings (each lasting 30 minutes or longer) occurred during the 45 testing nights, these provided 85 audio samples. The recordings from long awakenings showed the following percentages of occurrence for the more negative answers to the questions: (1) "not sleepy," 98% of 85 audio samples, (2) "reviewing and analyzing," 97%, (3) "worrying," 71%, (4) "body not relaxed," 60%, (5) "negative mood," 37%. It was expected that the responses would become progressively more negative over the duration of long awakenings. Content analysis, however, showed evidence of consistency in the subjective experience reports. During the majority of long awakenings (10 of 18), the answers to the set of five questions stayed exactly the same across the succeeding occasions for reporting (one per 10 minutes).
Conclusion: Useful self–report information about insomnia can be obtained during the sleep period with a small number of 20–second audio samples.

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An Investigation of Pre-Sleep Cognitive Arousal in Primary Insomnia, Delayed Sleep Phase Syndrome and Good Sleepers
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Introduction: Investigators have consistently reported a stronger association between cognitive arousal and primary insomnia (PI) than between physiological arousal and PI. This suggests that cognitive overarousal may be a predisposing, precipitating or maintaining factor in the aetiology or maintenance of PI. However, the pre-sleep cognitive arousal (PCA) associated with PI has primarily been investigated relative to good sleepers (GS). This is an important consideration. Comparing the PCA of individuals with PI to the PCA of GS does not explore the possibility that PCA may be a symptom of disordered sleep (or wakefulness) in general, rather than a symptom specific to PI. The purpose of this study was to investigate PCA in PI, delayed sleep phase syndrome (DSPS) and GS. DSPS, a circadian timing disorder that results in delayed sleep onset, but with no presumed cognitive pathway provides a suitable comparison group to investigate the possibility that PCA is epiphenomenal in PI.
Methods: Twenty-one male and 24 female (mean age = 19.8; sd = 1.2)campus recruited particpants meeting ICSD-R & DSM IV criteria for primary or psychophysiologic insomnia [PI (N=14), DSPS (N=14) and GS (N=17)] completed a range of questionnaires relevant to PCA and a 7-night sleep diary. Sleep diaries included subjective estimates of sleep onset latency, total sleep time, good or bad nights, attributions for good or bad nights and reports of pre-sleep thoughts.
Results: MANOVA yielded a significant main effect for questionnaire reported PCA indicating significant between group differences within this general construct of PCA [F (4.5,10) = 78; p = .000]. Univariate analysis demonstrated that PI and DSPS generally reported similar PCA greater than that of GS. Diary attributions and thoughts were categorized into environmental factors (ENV) (e.g. noise or procedure of experiment itself), somatic factors (SOM) (e.g. headache, tension, feeling too hot/cold), cognitive factors (COG) (efforts to fall asleep, latency to fall, planning, problem solving, rehearsing, reference to own type of thinking.) or Nothing/Cannot recall (NR). Percentages were calculated by dividing attributions or thoughts for each category by total number of attributions or thoughts for each group. Attributions: PI, DSPS and GS were most likely to attribute bad nights to COG (PI=84.6%, DSPS= 85.3%, GS = 61.5%). PI and GS were most likely to attribute good nights to SOM (PI=61.8, GS =64.4%) and DSPS were most likely to attribute good nights to SOM (53.2%) and COG (43.3%). Pre-Sleep thoughts: On Bad nights, PI and DSPS were most likely to report COG thoughts (PI=84.6%, DSPS = 85.3%), whereas GS reported COG thoughts (61.5%), NR (17.3%) or ENV (15.4%). On good nights, PI and GS were most likely to report COG thoughts (PI=87%, GS=87.6%) and

DSPS reported COG thoughts (78.5%) and NR (15.4%).
Conclusion: Results indicate that PI and DSPS groups experience similar levels of PCA greater than that of GS. Since there is no presumed cognitive pathway in the etiology of DSPS, this suggests that PCA may be epiphenomenal in PI. Results also suggest that individuals with PI attribute having difficulty falling asleep to cognitive factors, report thinking about cognitive factors while falling asleep, yet attribute not having difficulty falling asleep to somatic factors. Moreover, both GS and DSPS were much more likely to report thinking about NR when falling asleep than PI. Limitations of this study were that, despite careful diagnostic practices, individuals with DSPS might have had secondary symptoms of PI, or vice-versa. In addition, the possibility that DSPS report different types of attributions or thoughts when sleeping in/out-of phase was not investigated. Nevertheless, these novel findings have important implications for the study and treatment of PI and, by comparing the PCA of PI to another sleep disordered group, contribute to our understanding of symptoms specific to PI.

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Differential Autonomic Response to Audio Stimulation During Sleep in Primary Insomnia

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Introduction: Several indices of autonomic function indicate that patients with primary insomnia (PI) have increased sympathetic tone. Previous work has established that heart-rate, as in index of sympathetic tone, is elevated in PI, but it remains unclear what role this physiological hyperarousal plays in the genesis of the sleep pathology. To further examine this relationship, we assessed the acute autonomic response to audio stimulation during sleep in subjects with PI and matched controls.
Methods: Twenty patients with insomnia for at least 1 year, and twenty normal controls with comparable age and gender distribution were admitted to the laboratory for a 3-night protocol. Baseline PSG and MSLT recordings were obtained on the first day. On the second night, audio stimulation was applied through earphones using a calibrated tone generator (Grass Instruments, Braintree, MA). The waking audio threshold (WAT) was determined before lights out. After sleep onset, tones were applied during stage 2 NREM sleep beginning with WAT (=0dB) and increasing every 60 seconds (or after resumption of NREM Stage 2) at 10dB increments until the subject reported hearing the tone (audio arousal threshold; AAT). Subjects were then allowed to return to sleep. Between each sequence (every hour after lights out), subjects were awakened and kept awake for 10 minutes before being allowed to return to sleep. This allowed application of tones to comparable descending NREM Stage 2 in each sequence. The tone sequence was repeated four times over the first four hours of sleep. After the fourth awakening, subjects were allowed to return to sleep for the balance of the night. RR intervals were measured for 10 cardiac cycles before each tone, and 15 cardiac cycles after each tone using Grass Gamma software (Astromed-Grass, W.Warwick, RI). RR intervals were normalized using the average of the 10 cardiac cycles preceding each tone. AAT and changes in RR interval were compared for subjects with PI and controls using general linear model repeated measures assessments (Systat, SPSS, Inc).
Results: Consistent with previous work by others, we found no significant difference between PI and normal controls in AAT, although there was a trend towards lower AAT, particularly in the first two sequences (Mean AAT = 32.2 dB for PI; 39.7dB for controls; F(group x sequence)=2.56; p=.12). RR interval analysis showed the expected increase in heart-rate after each tone, the amplitude of which increased with increasing audio intensity. Although peak heart-rate did not differ at any stimulus intensity, PI subjects showed a prolonged heart-rate response for all stimuli, particularly at sub-threshold audio intensities (F (group x RRI) = 4.66, $p < .05$).
Conclusion: Heart-rate responses to audio stimulation differ between subjects with PI and normal controls. While the threshold for complete awakening did not differ significantly, the duration of the increase in heart-rate following each stimulus was substantially greater in PI. This was particularly true for sub-threshold stimuli that did not produce a full awakening. These data are consistent with the general model of autonomic hyperarousal in PI, and more specifically, with a decreased threshold for autonomic activation that may contribute to sleep disruption.

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Is Insomnia Associated With Fatigue After Controlling for Anxiety?

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Introduction: Mechanisms of increased fatigue have not been clearly delineated. Although people with insomnia report increased fatigue it is currently unknown whether this relationship is due to pathology associated with both insomnia and fatigue. For instance, anxiety is associated with both sleeping problems as well as higher levels of fatigue. In this study we obtained information on the self-reported mental and physical health of a randomly selected population in the metropolitan Memphis (TN) area. The subjects completed two weeks of sleep diaries, which affords us a thorough assessment of their sleep patterns. This investigation will assess the relationship between fatigue and insomnia after accounting for anxiety.
Methods: We used random-digit dialing to recruit at least 50 men and 50 women in each decade from 20 to 80+. Volunteers were paid between $15 and $200 (older adults were paid more) for completing 14 days of sleep diaries and questionnaires regarding daily functioning. We measured fatigue using Fatigue Severity Scale (FSS), and anxiety was assessed with the State Trait Anxiety Inventory (STAI). Insomnia criteria included a subjective sleep complaint plus a sleep pattern characterized by sleep latency > 31 minutes, or awake time during the night totaling > 31 minutes, at least three times per week for a six month duration.
Results: We have data on 772 participants, and 137 (17.7%) were diagnosed with insomnia. Correlations revealed significant relationships between insomnia and fatigue ($r = +.27$, $p < .01$), insomnia status and anxiety ($r = +.32$, $p < .01$), and anxiety and fatigue ($r = +.40$, $p < .01$). Results of a stepwise regression are as follows: 1) Anxiety explained 16% of the variance in fatigue ($p < .01$), and 2) After controlling for anxiety, insomnia status explained 2.2% of the variance of fatigue scores ($p < .01$).
Conclusion: Consistent with previous findings, anxiety, fatigue and insomnia status were significantly correlated. Insomnia explained a significant amount of variance even after accounting for anxiety. Due to the crossectional nature of the investigation, and the relatively small R the results should be considered with caution; however, insomnia appears to demonstrate at least a mild independent influence on fatigue.

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Characteristics of Individuals with Insomnia who Seek Treatment in a Clinical Setting Versus those who Volunteer for a Research Study

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Introduction: Controlled clinical trials of insomnia therapies tend to use fairly stringent criteria in the selection of study participants, with people who use medications and those with co-existing medical and psychiatric disorders being systematically excluded. Although such exclusion criteria yield more homogeneous samples and enhance scientific rigor, they may also limit the generalizability of the findings. The question arises whether a clinician can expect the same outcome with insomnia patients seen in clinical practice as those obtained in controlled clinical trials. One way to examine this issue of ecological validity is to compare the characteristics of individuals with insomnia who seek treatment in a clinical setting to those who volunteer to participate in a research study.
Methods: The clinical sample was composed of 106 consecutive adult patients (self- or physician-referred) who came to a private clinical psychological practice in Quebec City, with a predominant complaint of insomnia. The research sample was composed of 120 consecutive people who completed an initial assessment that determined their eligibility for a treatment study comparing the efficacy of cognitive-behavior therapy (CBT), singly or combined with medication, for insomnia. These people had been recruited primarily through advertisements. Demographic, health, psychological, and sleep variables were evaluated in both samples as part of the initial baseline assessment. The samples were compared using ANOVAs (continuous variables) and chi square tests (categorical variables); alpha was set at 0.05.
Results: The two samples were not significantly different with regard to gender, presence of a medical condition, number of prescription medications for conditions other than sleep, past history of psychopathology, presence of current anxiety disorder, age at onset of insomnia, duration of hypnotic use, and subjective (diaries) sleep onset latency, number of awakenings, sleep efficiency, and total sleep time. Significant differences between groups were observed on several other variables; the research sample was older, had a lower percentage of individuals on leave from work, a higher percent who were retired, a lower percent with current mood disorder, had lower anxiety and depression scores, longer duration of insomnia, lower ratings of perceived severity of insomnia, lower use of hypnotics, and longer time awake after sleep onset.
Conclusion: The research sample mimics the clinical sample on several important variables. For example, sleep diary measures, typically used in outcome research, were similar (except for time awake after sleep onset) in the two samples. In addition, rate of medical comorbidity was comparable. However, differences in psychological variables suggest the presence of greater distress in the clinical sample. These results are consistent with previous findings and provide some indication of the degree of resemblance between a clinical and a research sample of individuals with insomnia. This information is useful in the interpretation of research data for clinical use, and for the design of future studies where ecological validity is important.

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Dose Response Effects of Behavioral Insomnia Therapy: Final Report

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Introduction: Cognitive-behavioral insomnia therapy (CBT) has proven highly effective, but the number of CBT sessions needed to optimize outcomes remains unknown. This study was undertaken specifically to determine the optimal dose of CBT for treating primary sleep-maintenances insomnia.
Methods: Patients (ages 40-75 yrs.) were screened via structured interviews, medical examinations, and polysomnography. Those enrolled met criteria for Primary Insomnia and had an average wake time after sleep onset (WASO) > 60 minutes. Baseline assessment included sleep logs (2 weeks), actigraphy (one week), and multiple questionnaires. Baseline questionnaires were used to dichotomize the sample into Type 1 (low self-efficacy & high dysfunctional beliefs about sleep) and Type 2 (higher self-efficacy and low dysfunctional beliefs) subgroups. Patients within each subgroup were randomized to a waiting list control or to one (week 1 only), two (weeks 1 and 5), four (weeks 1, 3, 5 & 7), or eight (weekly) therapist-guided CBT sessions. Outcome data were derived from sleep logs, actigraphy, and questionnaires completed before, during, and 3 and 6 months following treatment.
Results: Eighty-six (43 women) patients (MAge = 55.5+/-9.8 yrs.) with significant sleep maintenance insomnia (Mbaseline WASO = 93.4 +/-44.5 min./night) were randomized to conditions. A 5 (condition) x 2 (Type) x 2 (gender) x 9 (time) x 9 (sleep log measures) MANOVA yielded a significant treatment x time ($F = 2.05$, $p = .008$) interaction. A 5 (dose) x 2 (Type) x 2 (gender) x 9 (time) x 4 (actigraph measures) MANOVA showed a significant ($F = 1.69$, $P = .004$) treatment x time x measure interaction. ANOVAs showed significant treatment x time interactions for log measures of WASO ($p = .02$) and sleep efficiency - SE ($p = .03$) and actigraphic measures of total wake time - TWT ($p = .002$) and SE ($p = .01$). Sleep logs suggested that 1- and 4-session protocols had greater efficacy than remaining conditions. Actigraphic TWT showed Type 1 patients benefited much more from the 1-session dose than did Type 2 patients who appeared to benefit most from the 4-session condition. Indicators of clinical improvement suggested the 4-session intervention was most effective overall. Of the patients receiving 4 sessions, 58.3% achieved at least a 50% reduction in WASO through treatment, whereas only 43.8% and 22.2% of those in the 1- and 2-session protocols respectively achieved this level of improvement. Of those with abnormal pre-treatment scores on an Insomnia Symptom Questionnaire (ISQ), normal post-treatment ISQ scores were obtained by 70% who received 4 CBT sessions, 53.4% who received 1 session, 38.5% who received 8 sessions, 26.7% who received 2 sessions and 0% in the waitlist condition. Follow-up data suggested the differences noted at the end of treatment generally endured through six months after treatment.
Conclusion: With sessions scheduled two weeks apart, a 4-session CBT protocol may afford patients sufficient therapist contact, yet provide ample opportunity to independently practice sleep-improving strategies. One or two CBT sessions may provide insufficient therapist contact, whereas high dose (8 weekly sessions) CBT may not foster proper therapist independence.

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Time Estimation in Chronic Insomnia Sufferers

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Introduction: It is well established that insomnia sufferers tend to overestimate their sleep-onset latency and to underestimate their total sleep duration, compared to polysomnographic data (PSG). These marked discrepancies are present in both insomnia sufferers and good sleepers, while they are significantly more pronounced in the first group. In spite of this, few studies have been carried out in order to determine if impaired time estimation may account for the tendency to misestimate sleep-wake parameters in insomnia sufferers. More interestingly, to our knowledge, no study has addressed this issue with a reliable and accurate time estimation task. Accordingly, this study compares the time estimation performance of chronic insomnia sufferers to that of good sleepers and evaluates the severity of sleep complaint in order to assess its association with time estimation performance.
Methods: The sample included 11 individuals suffering from chronic insomnia (7 women and 4 men, mean age = 44.64 years, SD = 12.71) and 11 good sleepers (5 women and 6 men, mean age = 48.00 years, SD = 7.86). All participants completed a time estimation task, namely a finger-tapping task, which consists of producing a series of taps separated by a duration corresponding to the target interval. Temporal intervals lasting 500-, 1,500- and 4,000- ms were presented. The order of the different time intervals were counterbalanced. Various outcome measures for each temporal intervals were derived, including the mean intertap intervals, the standard deviation of intertap intervals, the mean percent error rate, the mean coefficient of variation as well as the ratios. Severity of insomnia was evaluated through the Insomnia Severity Index (ISI).
Results: A MANOVA was computed on the time estimation data. Results indicate no significant between-group differences on time estimation data, Wilks' lambda = .50, F (12,5) = .412, p = .90. In addition, the multivariate ç2 based on Wilks' lambda was moderate, .50. Hence, time estimation did not differ between the two groups. There were no significant effect of order of presentation, nor any significant interaction between the groups and the order of presentation. As a consequence of these findings, follow-up tests to the MANOVA were not conducted on the dependent variables. Results of the correlational analyses used for the total sample suggest no significant relationship between severity of insomnia complaint and estimation of time.
Conclusion: The insomnia group was as accurate as the good sleeper groups and was not more prone to overestimate temporal intervals. In fact, there is no objective evidence of time estimation impairment in insomnia sufferers. Therefore, their typical misperception of sleep could not be explained by an altered sense of passage of time.

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Sleep Problems In The Taiwanese Army Recruits: A Cross-Sectional Survey Using Pittsburgh Sleep Quality Index

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Introduction: Two-year military service is an obligation for the healthy young male in Taiwan. Many of the recruits report the pressure and anticipatory anxiety before they physically enter the armed forces. We performed a survey for these recruits with Pittsburgh Sleep Quality Index (PSQI) in order to know their sleep condition and responses to such stresses.
Methods: A military training unit had been selected in random. In this unit, total 1092 recruits completed the PSQI questionnaire on the second day of their military service. Scores for PSQI global and seven subscales were computed and compared.
Results: 70% of the recruits reported moderately to severely bothered in the subscale of sleep quality; 66.9% of them needed more than 30 minutes to fall asleep. Average sleep duration was 7.35 hours and 67% of them had sleep efficiency lower than 85%. 52% reported the sleep disturbances for twice or more a week. 13.2% used sleeping medication and 50.8% had daytime dysfunction such as dozing, inattention or others. The average PSQI Global was 8.3 and more than 80% scored more than 5. Also, negative correlation was found between education years and sleep quality.
Conclusion: The results suggest that a significant proportion of the Taiwanese army recruits have poor sleep. Such sleep problems could be a reflection of anticipatory anxiety and stress responses relating to the military recruitment. PSQI is a useful and easy tool to measure the sleep quality and quantity.

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Mediators of Symptomatic Improvements Derived from Behavioral Insomnia Therapy

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Introduction: Cognitive-behavioral insomnia therapy (CBT) has proven highly effective for addressing the sleep/wake complaints of primary and secondary insomnia patients. Despite what is known about CBT treatment efficacy, little is known about the factors that mediate subjective objective improvements during the CBT treatment process. Hence, the current study was conducted to identify factors that mediate sleep and global symptomatic improvements resulting from CBT.
Methods: This study data were derived from 86 insomnia patients enrolled in a study designed to test one-, two-, four-, or eight-session CBT treatment protocols against a no-treatment control. During baseline study patients completed sleep logs (2 weeks), actigraphic monitoring (1 week) and several questionnaires including the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), the Insomnia Symptom Questionnaire (ISQ), a sleep-related Self-Efficacy Scale (SES), and the Positive and Negative Affect Scale (PANAS). Subsequently, patients underwent their respective treatment protocols. Each week of treatment they completed sleep logs and actigraphy as well as the ISQ and SES. At weeks 5 and 8 they also completed the SES and DBAS. At the end of treatment, patients were classified as improved if they showed a (1) > 50% reduction in baseline sleep log values of WASO; (2) > 30 minute/night reduction in baseline values of actigraphic TWT; and (3) a normal-range score of < 41 on the ISQ excluding those whose baseline ISQ score was < 41. For each of these indices, patients not meeting the criterion were labeled unimproved. Regression analyses were then used to predict each improvement criterion. Predictors included pre-post-treatment change scores for the positive and negative scales of the PANAS, a subset of DBAS items that compose the abbreviated DBAS-10 scale, and the SES.
Results: Modest, albeit significant, prediction of > 50% reductions in WASO was achieved on the basis of changes in SES scores (R2 =0.05, F = 4.56, p = .04). Subjects who were rated improved on WASO had greater increases in SES scores through treatment than did those who were unimproved by this criterion. A slightly higher level of prediction was achieved for the Actigraphic index of improvement (R2 =0.16, F =

7.71, p = .007). Prediction actigraphic improvement was related to changes on the PANAS negative affect scale. Those showing actigraphic improvement showed larger reductions on this scale than did those who were unimproved. Finally, improvement on the ISQ was strongly predicted (R2 =0.36, F = 16.97, p = .0001) by changes in both SES and DBAS10 scale scores with those rated as improved showing greater SES score increases and DBAS10 score declines than those rated unimproved.
Conclusion: Results suggest that increases in sleep-related self-efficacy and reductions in dysfunctional beliefs about sleep play a mediating role in the improvements seen in subjective sleep and global insomnia symptoms resulting from CBT. In contrast, objective sleep improvements appear dependent, in part, on reductions in negative affect. Further research is needed to determine if strategies designed to enhance changes in these mediators might enhance CBT treatment outcomes.

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Efficacy And Tolerability Of Indiplon-IR In The Treatment Of Transient Insomnia

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Introduction: Indiplon, a GABA potentiator with selectivity for receptors with the alpha1 sub-unit, is a new investigational therapy for insomnia. The immediate-release formulation of indiplon has a Tmax of approximately 1.5 h, and an elimination half-life of 1.5 h. The efficacy and tolerability of two doses of indiplon-IR were evaluated by polysomnography (PSG) in volunteers with clinically-induced transient insomnia.
Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate 10mg and 20mg doses of indiplon-IR in healthy volunteers, aged 21-64 years, with no history of insomnia (N=593; 62% female; mean age, 32 years). The laboratory adaptation model (first night effect), combined with a 2-hour phase advance, was implemented to induce transient insomnia in subjects who otherwise had a normal sleep pattern. PSG assessments of hypnotic effect included latency to persistent sleep (LPS) and total sleep time (TST); subjective assessments included latency to sleep onset (LSO), total sleep time (sTST), number of awakenings after sleep onset (sNAASO) and patient assessment of sleep quality on a 7 point scale. Next day residual effects were evaluated approximately 30 minutes after rise time by the Digit Symbol Substitution Test (DSST), Symbol Copying Test (SCT), and a Visual Analog Scale of Sleepiness (VAS).
Results: Mean LPS was significantly reduced on both indiplon-IR 10mg (21 min) and indiplon-IR 20mg (17 min) compared to placebo (33 min; p<0.0001 for both doses). Mean LSO was also significantly improved on both the 10mg dose (32 min) and 20mg dose (23 min) compared to placebo (40 min; p<0.0001 for both doses). TST, sleep efficiency, sTST, and sleep quality were all significantly improved on both doses of indiplon relative to placebo. There were no next-day residual effects as evidenced by the lack of difference between indiplon-IR and placebo on the DSST, SCT, or VAS. Adverse events for both treatment groups were similar to placebo, with no serious adverse events.
Conclusion: Indiplon-IR at doses of 10mg and 20mg induced rapid sleep onset compared to placebo as measured by both PSG and subjective measures. Both doses of indiplon-IR improved total sleep time, sleep efficiency, and perceived quality of sleep. No next day residual effect was detected. Indiplon is effective and well tolerated in inducing sleep in transient insomnia.

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Does Cognitive Behavioral Therapy for Insomnia Alter the Microstructure of NREM Sleep?

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Introduction: A number of studies suggest alterations of the sleep microstructure during NREM sleep in insomnia sufferers. The specific alterations vary across studies but are most often related to increased activity within the high-frequency components of the EEG spectrum (e.g., beta; 14-35 Hz). The efficacy of cognitive behavioral therapy (CBT) for insomnia has been assessed by evaluating its impact on sleep continuity as measured by subjective reports and polysomnographic recordings. However, the effect of CBT on the microstructure of NREM sleep has not been extensively evaluated yet. In the present study, the effects of the CBT on sleep microstructure are examined through the power spectral analysis (PSA) of the sleep EEG.
Methods: Participants were 13 individuals with insomnia (INS; 6 women, 7 men; mean age = 46.23 years, SD = 6.13) and 12 good sleepers (GS; 6 women, 6 men; mean age = 47.17 years, SD = 8.03) matched for age and gender. Individuals with INS were treated with CBT in a 6-week group format. Polysomnographic (PSG) recordings were conducted before (3 nights) and after CBT (2 nights). PSA was computed for stage 2 and slow wave sleep (SWS) of the first 4 sleep cycles of the second PSG night. Portions of the EEG containing artifacts were removed using visual and automated inspection. Absolute power was computed for 9 frequency bands : slow waves (0.00-1.00 Hz), delta (1.00-4.00 Hz), theta (4.00-7.00 Hz), alpha (7.00-11.00 Hz), sigma (11.00-14.00 Hz), beta 1 (14.00-20.00 Hz), beta 2 (20.00-35.00 Hz), gamma 1 (35.00-45.00 Hz) and gamma 2 (45.00-60.00 Hz).
Results: Results confirm the presence of impairments in the sleep microstructure of INS, including evidence of increased density for all frequency bands between 1.00 Hz and 60.00 Hz during stage 2 and for all frequency bands between 1.00 Hz and 35.00 Hz during SWS. There is no significant effect of CBT on the microstructure of stage 2 sleep. A global effect of CBT on the microstructure of SWS is noted but this effect does not translate in specific changes within any given rhythm. Improvements in sleep continuity parameters are correlated with increased density in the slow, theta, alpha, sigma and beta rhythms. Differences between INS and GS groups are still evident after CBT but those differences no longer reach significance.
Conclusion: The findings suggest that CBT may induce subtle changes in the sleep microstructure of insomnia sufferers. Increases in EEG activity within the lower and intermediate frequency bands of the EEG appear associated with improved sleep continuity. Whereas many studies suggest a potential contribution of the high-frequency activity to insomnia complaints both at sleep-onset and during the night, the present study emphasizes the possible involvement of the slow components of the EEG in sleep improvements after CBT. Future studies should also examine the effects of CBT on the microstructure of the EEG during the sleep onset period.

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How Daytime Sleepiness Results From Cognitive Arousal And Sleep Debt

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Introduction: A significant role for cognitive arousal in impeding sleep onset in insomniacs has been described previously. In the present study we investigated how cognitive arousal symptoms are related to the ability to fall asleep at bedtime and how it influences the ability to stay awake during the daytime in a sample of the general population.
Methods: 390 respondents with a mean age of 45.1 years (SD = 6.1) participated. 64% of the participants were females. Exclusion criteria were shift work, health problems requiring medical attention, and the use of CNS medication. Following self-report questionnaires were used: the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Inventory (PSQI), the Hyper-arousal Scale (HS), the Pre-Sleep Arousal Scale (PSAS). Structural equation modelling techniques were applied to determine the direct and indirect causal links between cognitive arousal (HS, PSAS), sleep latency at night (PSQI), sleep duration (PSQI) and daytime sleepiness (ESS).
Results: We retained a theoretically consistent model that yielded good fit indices, RMSEA = .044, CFI = .993 and TLI = .990, although the model remained statistically significant, Chi Square(86) = 150.526, p<.01. All standardized factor loadings in the model were significant (p<.001), and ranged from .44 to .86, suggesting that the indicators of the theoretical constructs were highly reliable. The standardized regression coefficients indicated that hyper-arousal traits were associated with pre-sleep arousal symptoms (?1 = .35; p<.001). Pre-sleep arousal caused an increase in sleep latency at night (?2 = .36; p<.001), as well as a decrease in absolute and relative amount of habitual sleep (hr of sleep and Sleep Sufficiency Index respectively) (?3 = -.36; p<.001). Less habitual sleep was also the consequence of extended sleep latencies (?4 = -.17; p<.05). Finally, a decrease in the amount of habitual sleep led to a higher level of daytime sleepiness (?5 = -.28; p<.001).
Conclusion: The present findings indicate that sleep tendency results from the combination of factors relating to sleep and to cognitive arousal. Firstly, sleep latency at night seemed to be primarily determined by cognitive arousal symptoms, in this way that higher levels of cognitive arousal were associated with longer sleep latencies at night. However, in contrary to what can be expected from classic models of sleep-wake regulation, smaller amounts of nightly sleep on a regular basis did not result in shorter sleep latencies at night. Secondly, for the tendency to fall asleep during daytime, quite the opposite was found. Here, in accordance with classic models of sleep-wake regulation, the tendency to fall asleep during the day was greater with less nightly sleep. On the other hand, higher levels of cognitive arousal were not related to a smaller tendency to fall asleep during the day. In conclusion cognitive arousal symptoms seem to particularly exert their influence in contexts of low exogenous arousal, such as at bedtime. As a consequence cognitive arousal only has an indirect effect on daytime sleepiness by its negative influence on sleep at night.

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Onset, Remission, Persistence, and Consistency of Insomnia Symptoms Over 10 Years: Longitudinal Results from the Wisconsin Sleep Cohort Study (WSCS)

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Introduction: Previous epidemiological studies in adults have demonstrated the high prevalence of insomnia symptoms. Many of these have distinguished between insomnia symptom types, i.e., sleep onset vs. sleep maintenance insomnia. Fewer studies have examined the course of insomnia over longer periods, or the consistency of specific insomnia symptoms. The aims of the current study were: 1) To examine the prevalence, onset, remission, and persistence of insomnia symptoms over 10 years in a well-characterized, representative population sample; and 2) To determine the consistency of specific insomnia types.
Methods: The WSCS on the natural history of sleep disorders includes a survey mailed to a random sample of state employees ages 30-65. 2319 subjects completed surveys at three time points: baseline (Survey 1); 2-5 years later (Survey 2); and 9-12 years later (Survey 3). Four self-report questions addressed insomnia: difficulty falling asleep, waking with difficulty returning to sleep, waking repeatedly during the night, and waking too early. Responses to each question used a 5-point frequency scale. We defined no insomnia as "never" or "rarely" (<one night/month) and insomnia as "often" or "almost always" (>5 nights/month). The two questions regarding middle of night awakenings were combined, leaving three insomnia types: sleep onset insomnia (SOI), sleep maintenance insomnia (SMI), and early morning awakening insomnia (EMAI). We estimated the prevalence of each specific insomnia type at each survey. We determined the percentage of subjects with new onset, remission, and persistence of insomnia across each survey interval. Finally, we examined the consistency of specific insomnia types among individuals who reported insomnia across all three surveys.
Results: Cross-sectional data from Surveys 1-3 showed that 21.4-26.2% of subjects reported no insomnia; 10.7-14.9% reported SOI; 27.9-37.6% reported SMI; 13.6-16.7% reported EMAI; and 34-44% reported at least one insomnia type. Longitudinal data averaged from Survey 1-2 and Survey 2-3 intervals showed that 13.1% of subjects reported no insomnia across two consecutive surveys; 3.1% reported new onset of insomnia; 1.8% reported remission of insomnia; and 24.2% reported persistence of any insomnia type. (57.9% of subjects reported other combinations of symptoms, including "sometimes" responses). Of the 895 individuals with insomnia at Survey 1, 404 (45%; 17% of the total sample) reported persistent insomnia at both Survey 2 and 3. Among these 404 individuals, 0.1% reported only SOI across three surveys, 17% reported only SMI, and 0.1% reported only EMAI. By contrast, 40% endorsed each of the three insomnia types and 43% endorsed two insomnia types during at least one of the three surveys.
Conclusion: Consistent with previous studies, we found high prevalence of insomnia symptoms in a middle-aged adult population. The rate of new onset insomnia was low, but almost twice as high as the remission rate. Compared to incidence and remission, we found a very high rate of persistent insomnia over 5 and 10-year follow-up periods. The large majority of subjects with persistent insomnia had a combination of two or more insomnia types. This strongly suggests that specific insomnia symptoms vary over time and should not constitute a basis for classifying subjects.

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Randomized Intention to Treat Trial of Nurse-administered Cognitive Behavior Therapy (CBT) for Insomnia in General Medical Practice

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Introduction: Persistent insomnia is a common complaint in general practice. Several meta-analyses indicate that behavioral and cognitive behavioral therapies (CBT) are efficacious in reducing symptomatic sleep complaint and in improving sleep quality. The primary care physician, however, needs to know whether such treatments are likely to benefit typical cases in routine practice. Characteristics of such samples often differ from those entering research trials. Furthermore, practitioners need to know that it is possible to deliver CBT in practice to the large number of clients who may benefit. We have previously reported clinical effectiveness data using our manualised CBT programme, delivered by Health Visitors (HV; primary care community nurses). The present study extends this work. Our aim was to investigate whether or not CBT could be disseminated widely and effectively to a realtively unselected population.

Methods: The study comprised a randomised intention to treat trial of CBT versus treatment as usual (TAU). Assignment to condition was by an independent person. Participants met ICSD-R/DSM-IV criteria for psychophysiologic/primary insomnia. Only those with severe, untreated psychopathology and other suspected sleep disorders were excluded. Sleep diary and wrist actigraphy data were collected for two weeks prior to treatment and for two weeks at post-treatment along with other questionnaire measures. CBT comprised five, weekly 50 minute group sessions (4-6 persons per group) conducted by a HV following a standard protocol. CBT included sleep education, stimulus control, sleep restriction, cognitive restructuring and paradoxical intention.

Results: Of 385 persons screend, 251 (78M, 173F; mean age = 53.4 yr) met criteria and consented to participate in the intention to treat trial (135 CBT, 116 TAU). Average duration of insomnia was 10.8 years. Sleep diary data revealed that at post-treatment CBT participants had a significant mean reduction in SOL of 29.9 min. and in WASO of 53.8 min (1.6 min. increase, 11.4 reduction in TAU) [$p < .0001$]. On the Pittsburgh Sleep Quality Index, CBT participants significantly reduced mean scores, from 12.4 to 9.7, whereas TAU participants did not (12.0 - 11.4) [$p < .0001$]. Actigraphic measurement of sleep parameters, however, did not reveal any improvement in sleep in either group, and actigraphy did not correlate significantly with subjective report. Other self-report measurements indicated significant reductions under CBT compared with TAU; eg. Dysfunctional Beliefs and Attitudes About Sleep, Glasgow Content of Thoughts Inventory [both $p < .0001$].

Conclusion: CBT appears to be clinically effective for insomnia in routine care. These results are comparable with meta-analyses of more selected populations. Actigraphic measurement appears unsuitable as a measure of insomnia because it does not correlate with clinical complaint and does not demonstrate improvement parallel to subjective improvement. Further analyses of our dataset will be possible to explore health economic indices and possible predictors of improvement.

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Heart Rate Variability In Patients With Insomnia And Good Sleeper Controls

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Introduction: Very little work has been undertaken using heart rate variability (HRV) as a measure of sympathetic and parasympathetic activity in pateints with insomnia. The most recent study by Bonnet et al. found that pateints with insomnia exhbited increased parasympathetic and decreased sympathetic modulation of HR compared to good sleepers (GS) across nonrem (NR) stages and in rem (R) and wake (W). The goal of this pilot study is to investigate the difference between patients diagnosed with primary insomni (PI) and good sleepers (GS) on measures of HRV for each stage of sleep during the first NR cycle (S1, S2, S3, S4), R cycle, and W.

Methods: Data were obtained from 20 gender (7 females, 3 males per group), age (PI: 44.1(14.9); GS: 44.0(14.0)), and BMI (PI: 26.6(5.5); GS: 26.1(5.5)) matched volunteers participating in ongoing studies at the University of Rochester. None of the participants evidenced any sleep disordered breathing. All data were derived from the first night of polysomnographic study where ECG samples were extracted from the first 30 seconds of uninterupted sleep for each stage of NR, R and W. The ECGs were scanned utilizing a scanner written in DOS/C. Time and frequency domain HRV indices and nonlinear HRV indices were computed for each of the 30s interbeat interval files. NR HRV was also computed as the average over stages S1, S2, S3, and S4 for each HRV index. Data were log-transformed (log1.0+ var-varmin) for normality, and unpaired, unequal-variance t-tests utilized. PNN50 is the percent of adjacent intervals of normal beats differing by more than 50ms and is considered a measure of modulation of HR by the parasmpathetic nervous system. AVNN, the average of all intervals between normal beats, is the heart period, a measure of arousal. Low frequency spectral power (LF), from 0.04Hz to 1.5Hz, represents mixed sympathetic and parasympathetic activity. High frequency spectral power (HF), from 0.15Hz to 0.4Hz, represents parasympathetic activity. The ratio LF/HF, represents smypathovagal balance and, arguably, sympathetic activity. The ratio LF/(LF HF), or normalized LF power, also reflects sympathetic activity.+

Results: Mean log(PNN50) was significantly greater for GS vs. PI in W and S1: $p=0.046$ and $p=0.022$, respectively. Log(AVNN) was greater for GS vs. PI for NR only, but not significantly ($p=0.071$). For NR, mean log(LF/HF) and log(LF/(LF HF)) were significantly greater for GS vs. PI: $p=0.030$ and $p=0.021$, respectively.

Conclusion: PI have significantly decreased parasympathetic activity in W and S1. This decrease remained but was no longer significant as stages of deeper sleep were entered. The decreased values for indices reflecting relative sympathetic activity in NR for PI vs. GS are in qualitative agreement with the findings of Bonnet et al. Our preliminary findings are consistent with findings from quantitative EEG data, which demonstrate increased cortical arousal in PI. Accordingly, the lower PNN50 in our sample suggests an inhibition or blunting of parasympathetic activity, which would correspond to the heightened arousal evidenced in many patients with PI. In addition, in this study, PNN50 was a more sensitive index of arousal than AVNN. Due perhap to methodological differences, the results of this pilot study are not in complete agreement with the findings of Bonnet et al. The decrease in PNN50 in PI, however, is a new finding.

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An Exploratory Validation of Actigraphic Measures of Insomnia

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Introduction: Actigraphic and polysomnographic measures of sleep have been strongly correlated in normal sleepers and in sleepers with apnea, but few actigraphy validation studies have been conducted on people with insomnia (PWI). This investigation will focus on whether or not changes in sleep values (sleep onset latency [SOL], number of awakenings [NWAK], wake after sleep onset [WASO], total sleep time [TST], and sleep efficiency [SE]) covary between instruments and whether or not the instruments produce significantly different sleep values.
Methods: Ten participants with insomnia between the ages of 24 and 61, living in the Memphis area were recruited from a pool of volunteers. One participant was disqualified due to significant sleep apnea detected by PSG. Data on 30 or 40 research participants will be available by meeting time. Participants were offered 4 free behavioral treatments for insomnia for completing two weeks of sleep diaries and daytime functioning questionnaires and for spending one night at the sleep disorders center at which time their sleep was simultaneously measured using Actiwatch-64 and PSG. Because actigraphy tends to overscore sleep in people with insomnia, who lie awake motionless, the actigraphic values were analyzed using a high sensitivity threshold that infers sleep from minimal limb movement.
Results: The Pearson r's for actigraphy and PSG on each sleep variable revealed a significant correlation on TST, r = .827, p = .006. The range of r values on the sleep variables was between .167 and .827. According to the paired t-tests, the instruments do not produce significantly different sleep values although these are low power tests due to low n.
Conclusion: Strong correlations between actigraphy and PSG would show that the two measures are varying consistently across participants. We demonstrated this for TST only. Failure to find significant differences between actigraphy and PSG mean sleep values supports the conclusion that actigraphy values closely mirror PSG values. Reporting the results in more detail at this time could be misleading due to small sample size. A more detailed discussion of results from a larger sample size will be presented by the conference date.

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Consequences Of Insomnia On Professional Activity In The Paris Region

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Introduction: Introduction: The consequences of chronic insomnia on daytime functioning and especially the professional consequences are of crucial importance, e.g. absenteeism, accidents, errors, productivity and career advancement. The main goal of the study was to compare absenteeism based on objective data given by the personnel departments of the firms, between insomniac employees and good sleeper employees matched for age, sex and socio-professional category (manager / employee / worker).
Methods: Methods: A case-control study was conducted by 32 occupational physicians, involving 738 permanent daytime workers from the Paris region (average age of 44 years, 64% of female), who were assigned to the insomniacs group or the good sleepers group, according to DSM IV criteria for insomnia evaluated during the last 2 years. The complete questionnaire included socio-demographic parameters, professional criteria, the Spiegel questionnaire, and the Pittsburgh questionnaire (PSQI sleep disorder severity), measures of absenteeism, driving accidents and errors at work during the last two years, as well as career advancement, efficiency, attitude and initiatives at work. Analyses were performed using SAS software with two-tailed tests (t test, Wilcoxon, Kruskall-Wallis or Fisher exact tests, depending on parameter and distribution).
Results: Results: Insomniac employees were statistically different from good sleeper employees regarding the Spiegel questionnaire (2.7+/-0.8 vs 4.2+/-0.5, mean+/-sd, $p<0.001$) and the Pittsburgh questionnaire (11.7+/-3.0 vs 4.4+/- 1.8, $p<0.001$). The consequences on work performance were a higher duration of absenteeism for the insomniacs (11.7 +/- 22.3 days vs 4.8+/-10.4, $p<0.001$). The main reasons for absenteeism were fatigue (11%), influenza (7%), and gastroenteritis (7%). The absenteeism was lower for managers (6 days vs 9 days for employees, $p<0.001$) and for males (7 days vs 9 days, $p=0.002$), the difference between groups remaining statistically significant after adjustment for socio-professional category or gender. The prevalence of driving accidents (15%) and the number of accidents were not different between groups. Errors at work were more prevalent in insomniac employees (44.0% vs 31.3%, $p<0.001$), with a lower efficiency (73.9% vs 89.7%, $p<0.001$), and a poorer career advancement (56.4% vs 68.6%, $p=0.004$). We also noted significant differences on attention, attitude and initiatives at work, relationships with clients or colleagues, with a better evaluation for good sleeper employees.
Conclusion: Conclusions: The results of this case-control study indicated a clear negative impact of chronic insomnia on professional activity.

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Vulnerability to Chronic Insomnia:A Longitudinal Population-based Prospective Study

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Introduction: Recent research has demonstrated that a subset of normal healthy individuals with sleep comparable to that of the general population are differentially vulnerable to acute sleep disturbance induced by pharmacological, psychological, and environmental challenges. Following sleep-related challenges such as a first night in the laboratory, these otherwise normal individuals show evidence of physiological hyperarousal similar to that seen in individuals with primary insomnia. However, no studies have tested whether this vulnerability to acute stress-induced sleep disturbance may represent a predisposition to the subsequent development of chronic insomnia. The goal of this study was to test the hypothesis that healthy normal sleepers who demonstrate an elevated vulnerability to challenge-induced acute sleep disturbance are at increased risk for the subsequent development of chronic insomnia.
Methods: The subjects for this study were a prospectively assessed sample drawn from the general population of tri-county metropolitan Detroit (n = 173; age = 44.2 ± 12.3 years; 46% Female). All individuals meeting DSM-IV based lifetime criteria for insomnia were excluded (n = 29). Subjects completed the Ford Insomnia Response to Stress Test (FIRST), a validated measure of individual vulnerability to stress-induced sleep disturbance (n = 144; age = 44.7 ± 12.0; 44.4% female). The sample was divided into those scoring high and low (median split) on the FIRST. Each group was re-assessed approximately 13 months later (mean 391.3 ± 42.1 days) regarding insomnia using criteria identical to that used for

exclusionary purposes during the initial assessment. Relative risk (RR) for the incidence of insomnia over the entire follow-up period was compared for individuals scoring high and low on the FIRST at Time 1.
Results: As expected, after the exclusion of individuals meeting insomnia criteria at time 1, individuals with high FIRST scores reported nightly habitual sleep times that were comparable to individuals with low FIRST scores (406.4 ± 73.0 min; 395.2 ± 75.6 min, respectively; p = n.s.). At the end of the ~13 month follow-up period, a total of 12 individuals now met criteria for insomnia (8.3% incidence rate). In addition, individuals who developed insomnia now reported significantly lower nightly total sleep time compared to those individuals who continued not to report insomnia (358.9 ± 47.2 min vs. 399.7 ± 70.8 min; t(140) = -1.95, p = .05). Importantly, the risk for developing insomnia during the follow-up period was significantly greater for individuals with high vs. low FIRST scores at Time 1 (RR = 1.77, 95% C.I. = 1.21 - 2.59).
Conclusion: This prospective longitudinal population-based study supports the hypothesis that "normal" individuals without insomnia, who are nevertheless vulnerable to transient stress-related sleep disturbance, are at greater risk for the subsequent development of chronic insomnia. Future research is needed to determine the biological mechanisms associated with this diathesis of underlying vulnerability to acute sleep disturbance, as well as the processes involved in the evolution of transient to chronic insomnia.

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Prevalence Of Insomnia, Types Of Strategies And Consultations Initiated, And Determinants Of Help-Seeking Behaviors

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Introduction: Despite the high prevalence and burden of insomnia, only a small proportion of insomnia sufferers seeks treatment for this condition. There is little information about the determinants of help-seeking behaviors, and about the types of resources and strategies people employ to alleviate insomnia symptoms. The objective of this study was to estimate the prevalence of insomnia and document the types of strategies used and consultations initiated for sleep disturbances.
Methods: A telephone survey was conducted in the fall of 2002 to identify a sample for a longitudinal study of insomnia risk factors. The target population consisted of all French-speaking residents of the province of Quebec, Canada, aged 18 years and older . A representative sample was obtained using a random digit dialing method programmed to generate geographically stratified phone numbers. Of the 5991 persons contacted, 2001 (33.4%) completed the telephone interview. The mean age of the participants was 44.7 years old (SD = 16.1, range 18-91 years) and 58% were women.
Results: Of the total sample, 25.3% were dissatisfied with their sleep, 29.9% presented at least one insomnia symptom (early, middle, late insomnia) at least three nights a week, and 9.4% met criteria for an insomnia syndrome (i.e., insomnia with daytime consequences and/or distress). Mixed insomnia was the most prevalent condition (12.8%), followed by sleep onset insomnia (8.7%). The combination of sleep dissatisfaction and the presence of one insomnia symptom were present in 16.9% of the sample. Conversely, 62% of the participants were satisfied with their sleep and had no insomnia symptoms, while 13% reported being satisfied with their sleep despite the presence of one insomnia symptom. There was 12.7% of the sample who had consulted a health-professional at least once in their life for sleep problems. The majority of those had consulted a general practitioner (83%), followed by other specialists (16 %), and psychologists (6%). The main determinants for consulting included fatigue (48%), psychological distress (40%), suggestion from a relative or a health-professional (24%), physical malaise (22%), and work impairment due to poor sleep (14%). Several strategies other than medication had been used in the past year to alleviate insomnia: reading (34%), music (25%), and relaxation (21%). In addition, natural (herbal/dietary) products were used by more people to promote sleep than prescribed medications (16% vs. 11%). Finally, alcohol and over-the-counter medication were each used by 4% of the sample.
Conclusion: These findings confirm the high prevalence of insomnia in the general population. In addition, while only a small percentage of insomnia sufferers seek professional treatment for this condition, many individuals initiate a variety of self-help strategies, particularly when daytime consequences become more perceptible. Longitudinal follow-ups are being conducted to gather more information about treatment seeking behaviors and to examine the natural history of untreated insomnia.

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Pharmacokinetic Profile Of A New Modified-Release Formulation Of Zolpidem Designed To Improve Sleep Maintenance

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Introduction: The objective of the study was to compare the plasma pharmacokinetic profile of zolpidem administered as a new 12.5 mg modified-release formulation (zolpidem-MR = test) with that of the current reference marketed imediate release 10 mg product (reference) after single oral administration.
Methods: This was a randomized, open, cross-over study in 24 healthy male volonteers aged 18 to 45 years. Subjects received single doses of the two oral formulations in fasting conditions and one intravenous infusion (8 mg, 30 minutes). Zolpidem plasma concentrations were measured up to 16 hours after oral administration and up to 12 hours after intravenous administration (n=18 samples per period) using a validated LC-MS/MS method. Calculation of pharmacokinetic parameters was conducted with a non-compartmental analysis. The two oral formulations were compared by calculating ratio point estimates of the relevant pharmacokinetic parameters (test versus reference) and their 90 % confidence intervals. In vivo release absorption profiles were obtained by deconvolution using the intravenous profile as reference.
Results: For the two oral formulations, the absorption is quite rapid, with maximal plasma concentrations being observed 0.88 to 1.5 hours after administration (median values). No statistically significant difference could be shown between Tmax values obtained with these two formulations. The Cmax was lower with zolpidem-MR compared to the reference formulation (point estimate of 0.82). Plasma concentrations of zolpidem observed after administration of zolpidem-MR were maintained above those observed with the reference for a longer period of time and particularly from 3 up to 6 hours post dose. This was confirmed by an increase in the HVD (Half Value Duration i.e. time during which plasma concentrations are equal to 50% of Cmax) from 2.3 to 4.6 hours, for the reference and the test formulations, respectively. The in vivo release absorption profile of zolpidem-MR was consistent with in vitro findings. No loss of bioavailability (F) due to the modified release characteristics of zolpidem-MR was observed, as compared to the reference. The terminal half-life was similar for the two formulations with respective values of 2.8 and 2.6 hours, for zolpidem-MR and for the reference.
Conclusion: All these results show that this new modified release formulation provides the appropriate pharmacokinetic characteristics to extend plasma concentrations into the middle of the night (3-6 hours post

dose). Overall, the safety profile of zolpidem was good and comparable between the two oral formulations. According to PK data, the onset of action of zolpidem-MR is expected to be the same as the marketed product (no difference in terms of Tmax) and zolpidem-MR should show a better sleep maintenance into the middle of the night as compared to the marketed product.

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Insomnia And Lunar Phases: Is There A Relationship?

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Introduction: Popular beliefs exist that lunar phases might influence sleep wake cycles. Patients with insomnia often report that their sleep is worse on nights with a full moon or a new moon. Belief in such a relationship could result in a self-fulfilling prophecy and contribute to perpetuate insomnia. Studies in other fields have investigated the relationship of lunar phases to incidence on cardiac arrests, seizures, violent/disruptive behaviors, and psychiatric consultations or hospital admissions. None of these studies found a significant relationships. The present study examined whether lunar phases are related to insomnia.
Methods: The sample consisted of 106 participants (57.6% women, mean age = 45.5) who were evaluated for insomnia treatment studies. Participants met diagnostic criteria for primary chronic insomnia (mean duration of 12.8 years). They completed daily sleep diaries for an average of 31 days (SD = 12) before receiving treatment. Nightly values for sleep efficiency (SE), sleep onset latency (SOL), and wake after sleep onset (WASO) were derived from the sleep diary. An insomnia night was defined as (a) SOL and/or WASO higher or equal to 60 minutes, and (b) SE smaller than or equal to 80%. Data for the lunar cycle (0% - new moon to 100% - full moon) were extracted from Moon Calculator software (version 6; Ahmed, 2001) for each participant according to the date of each night recorded in their sleep diary.
Results: Three types of analyses were conducted. First, Pearson correlation coefficients were computed between moon cycles, SOL, WASO, and SE parameters for each participant. Based on standard meta-analytic procedures, all individual coefficients were transformed and averaged to test the existence of significant relationships between moon cycles and sleep parameters. Results showed that the average correlation between moon cycle and sleep was r = 0.04 (p = .08) for SOL, r = 0.02 (p = .43) for WASO, and r = -0.02 (p = .37) for SE. Second, sleep parameters were then compared between new moon, half-moon (waning or waxing), and full moon phases. Mixed models with a within-subject effect (moon) revealed no significant differences for SOL (p = .91), WASO (p = .16), and SE (p = .22). Finally, the percentage of insomnia nights was compared across moon phases. Descriptive statistics suggested that the probability of experiencing insomnia was higher during the new moon (Pr = .480) and the full moon (Pr = .537) compared to half-moon (Pr = .445). However, a mixed model with a within-subject effect (moon) failed to reveal a significant difference, $F(2,182) = 1.75$, $p = 0.18$.
Conclusion: These findings indicate that the lunar cycle is not significantly related to sleep and sleep disturbances; in other words, there is no evidence of an ultradian cycle in sleep disturbances that would parallel the lunar cycle. Despite, a trend suggesting that individuals with chronic primary insomnia are more likely to experience poor sleep during full moon, the magnitude of this effect was small (d = 0.1 to 0.3). An interesting follow up question would be to examine if the relationship between sleep and lunar cycles is more likely to be found among those who actually endorse the belief of such a relationship.

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Insomnia: Functional Neuroimaging Evidence for Hyperarousal

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Introduction: To investigate the neurobiological basis of poor sleep and daytime fatigue in insomnia, we assessed regional cerebral metabolism in insomnia patients during waking and NREM sleep. We hypothesized that insomnia patients would have an increase in whole brain metabolism during both waking and sleep; that the sleep difficulties of insomnia patients may be the result of a failure of wake promoting brain structures to decline in metabolism from waking to sleep; and that the daytime fatigue of insomnia patients may be explained by reductions in waking metabolism in thalamocortical networks, especially prefrontal cortex, given that such changes have been seen following sleep deprivation.
Methods: Insomnia patients (n=7) and healthy subjects (n=20) completed regional cerebral glucose metabolic assessments during both waking and NREM sleep using [18F]fluoro-2-deoxy-D-glucose positron emission tomography (PET).
Results: Insomnia patients showed increased cerebral glucose metabolism during sleep and wakefulness; a smaller decline in relative metabolism from wakefulness to sleep in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate and medial prefrontal cortex; and decreased relative metabolism in the prefrontal cortex during wakefulness.
Conclusion: Subjectively disturbed sleep in insomnia patients is associated with increased brain metabolism. Their inability to fall asleep may be related to a failure of arousal mechanisms to decline in activity from waking to sleep. Further, their daytime fatigue may reflect decreased activity in prefrontal cortex that results from inefficient sleep.

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First Night Effect in Healthy Individuals: Association with Age, BMI, and MMPI Profiles

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Introduction: First night effect is a well-described phenomenon of sleep disturbance occurring in healthy individuals during the first night of recording in the sleep laboratory. The variables that determine the extent of this reaction are not well-studied. The goal of this study was to assess whether age, gender, obesity, and personality characteristics are associated with the degree of sleep disturbance.
Methods: Eighty, healthy, normal sleepers (60 men, 20 women) of a wide age range (mean ±SD, 36.4 ± 16.9, 18 to 76 years) and Body Mass Index (26.4 ± 5.5, range 18.8 to 54) were participants in studies that included three consecutive nights in the sleep laboratory. The subjects had thorough medical and psychiatric evaluations, a detailed sleep history, routine blood tests, urine drug screen, and completed a Minnesota Multiphasic Personality Inventory-Second Edition (MMPI-2). A linear regression analysis was used to predict the change from night one to night two on 7 key sleep variables. Predictors included age, BMI, gen-

der, and the 8 clinical scales of the MMPI.
Results: The main predictor of the change of sleep latency, wake time after sleep onset, and percent sleep time was the hypochondriasis scale (Hs) of the MMPI. The change of REM sleep and REM latency was primarily determined by degree of obesity (BMI). Finally, the change in amount of slow wave sleep and stage 1 sleep was primarily determined by age. The same results were obtained when we used the difference of night 1 - night 2 or the average of nights 2 and 3, or when we adjusted for the difference between nights 1 and 2 by using sleep variables of night 3 as a surrogate of baseline sleep.
Conclusion: The first night effect is stronger in the older, the obese, and those that have excessive concerns about health issues. It appears that sleep disturbance related to sleeping in a foreign environment is associated with both physiological and psychological factors. Further studies are needed to clarify whether this transient sleep disturbance is a marker for risk of developing insomnia in the future.

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Yawning As Therapy? The Role Of Yawning In Sleep Disorders

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Introduction: The theory of yawning as a respiratory phenomenon has been discredited, but its function remains unknown. It appears to be a method of modifying cortical arousal, associated with arousal as well as de-arousal. Yawning and stretching in the morning engages wakefulness, while the temporary autonomic and EEG arousal that occurs in the 15 minutes subsequent to yawning staves off drowsiness before bedtime and during circadian dips in alertness. Yawning is a universal and paralinguistic signal of drowsiness and is also contagious. Seeing others yawn elicits an involuntary yawn, as does reading, thinking or hearing about yawning. Clinically yawing has only been studied where it is pathological, mainly in CNS disorders. How yawning relates to sleep and insomnia is unknown. Around 10% of the adult population have insomnia, but there are few treatments that do not involve sleeping pills. Contemporary models of insomnia are based around arousal modulation, with insomniacs appearing hyperaroused relative to good sleepers. It is this link that suggests that yawning could be used in a form of therapy for insomnia that is universal, inexpensive and easy to administer. How yawning relates to sleep in a normal population, and how that differs from Primary Insomniacs, needs to be investigated before a therapy can be developed.
Methods: There are 4 stages prior to a new treatment being piloted. The first uses a questionnaire about beliefs and perceptions of yawning. The second is uses actigraphy and sleep diaries to obtain sleep efficiency and circadian rhythm measures. The third involves combining behavioural and physiological data to measure a yawn with repeatability, specificity and sensitivity. The fourth involves identifying a reliable and repeatable trigger to evoke yawning. Once established the trigger will be used to evoke yawns so physiology can be monitored. This will be incorporated into Multiple Sleep Latency Test paradigms. Upon reaching this stage single case experiments will be conducted on Primary Insomniacs to investigate the effects of evoking yawns as part of an intervention.
Results: At the time of writing 3 of the 4 stages were underway. Initial responses to questionnaires indicates the pattern of yawing follows the circadian prediction. Early actigraphy data backs up this pattern. The causes of yawning are related to tiredness, heat or ill-ventilated rooms, and most people assume that yawning indicates tiredness or boredom and is related to oxygen intake. Physiological measurements indicate that a yawn can be easily identified by using a combination of EEG, EMG (masseter and sub-mental muscles), respiration, ECG and oximetry. Using these measures a yawn can be discriminated from a cough, sigh, laugh or other behavioural action. Early indications show that showing subjects a video of ten 8 second clips of someone yawning interspersed with 5 seconds of blank screen will evoke yawns in around 65% of subjects within 5 minutes of observing the tape.
Conclusion: Early results indicate that we can easily evoke and measure yawns in subjects. The next stage is to determine if there are population differences in the frequency, occurrence and perception of yawns between Good Sleepers and Primary Insomniacs.

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Sleep Hygiene Practices in Insomniacs and Matched Controls in the General Population

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Introduction: Clinical trials using sleep hygiene to treat insomnia have focused on a variety of behaviors and have produced equivocal results. Importantly, the efficacy of this therapy is contingent upon basal poor sleep hygiene, yet, there are few data from the general population evaluating specific sleep hygiene practices in individuals with insomnia. Thus, it is not known which, if any, specific behaviors related to sleep hygiene are linked to reports of insomnia. This study was designed to assess specific aspects of sleep hygiene in individuals with insomnia and age and sex matched controls both drawn from the general population.
Methods: A random sample of individuals meeting DSM-IV based criteria for insomnia (primary or secondary) was selected from the Detroit tri-county population. Each insomniac in the sample was paired with a randomly selected age and sex matched control also drawn from the general population (insomnia n=258, control n=258; mean age=43 ± 11 years; 62% Female). Criteria for insomnia included sometimes or often experiencing difficulty getting to sleep, staying asleep, or having non-refreshing sleep for at least one month and severity >6 (scale=0-10). Shift workers were excluded. Sleep hygiene was measured by overall cigarette smoking and smoking near bedtime, overall alcohol use and alcohol use for sleep, caffeine use, napping, time in bed, and reported likelihood of sleeping in on weekends.
Results: Insomniacs reported an increased frequency of smoking compared to controls (40.7% vs. 22.9%, Chi-Square= 18.9, p=.001). Within regular smokers (past two weeks), insomniacs also reported more frequently smoking within five minutes of bedtime (45.3% vs. 21.8%, Chi-Square= 8.25, p = .004). Insomniacs reported more alcohol use (drinks/week) [4.7 ± 11.0 vs. 2.3 ± 4.8; t (512)=3.0, p = .003] and reported more use of alcohol for sleep (29.1% vs. 11.2%, Chi-Square=25.5, p= .001). Within regular drinkers (past two weeks), insomniacs more frequently reported using alcohol less than 30 minutes before bedtime (12.9% vs. 5.6%; Chi-Square=3.96, p = .05). Caffeine intake (drinks/day) did not differ between groups (3.0 ± 4.0 vs. 2.7 ± 3.3, p= n.s.). Insomniacs reported a higher frequency of naps per week (3.5 ± 4.5 vs. 2.7 ± 3.5; t(512)= 2.4, p =.02). Hours spent in bed did not differ between groups (weekday: Insomnia= 7.3 ± 1.9, controls= 7.4 ± 1.2; weekend: Insomnia= 7.8 ± 2.0, controls= 8.03 ± 1.4; p = n.s.). Despite comparable times in bed, insomniacs were more likely to report sleeping in on weekends (42.7% vs. 32.4%, Chi-Square=5.7, p= .02).
Conclusion: This is the first study to demonstrate that individuals

reporting insomnia do, in fact, frequently engage in more inappropriate sleep hygiene practices than do non-insomniacs. While established behavioral treatment regimens frequently employ a general component addressing sleep hygiene for insomnia patients, the present results suggest that particular sleep hygiene practices that are engaged in by insomniacs may be worthy of increased attention. Specifically, smoking, alcohol use, and compensatory sleep (i.e., naps and sleeping in on weekends) may be more important treatment targets in comparison to time spent in bed and caffeine intake.

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Sleep Onset Process Abnormalities In Primary Insomnia

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Introduction: Conventional EEG analysis provides inconsistent data to explain complaints and poor sleep in primary insomnia. New methods of analyzing EEG data are needed. Studies have shown that insomnia patients have higher beta and lower delta power during sleep, but have not studied the sleep onset process in detail. This study's aims were 1) to test prototype rules for hand-scoring 4-second epochs, and 2) to describe abnormalities in the sleep onset processes of primary insomnia patients using these new rules, and as a time series of EEG power spectra.
Methods: Archival PSG records from 12 primary insomnia subjects and 12 individually age- and sex-matched controls were tested for group differences in conventional PSG parameters. Under blinded conditions, 4-second epochs of the initial sleep onset were scored for sleep-wake state (Wake, non-REM, or REM) and presence of artifact (yes/no) using a set of prototype scoring rules. A scoring reliability study was performed with kappa statistics. Group differences in number of sleep and artifact epochs were tested with Mantel-Haenzel X2 tests. Group differences in time until stable sleep (2 minutes of continuous non-REM) were tested with Kaplan-Meier analysis. Power spectra of each 4 second epoch were obtained to derive power amplitudes in conventional frequency bins. Linear mixed effects (LME) time-series models terms were constructed for the 5 minutes before and after sleep onset (identified by the conventional PSG scoring), to examine for group differences in delta (0.5-4 Hz) and beta (17-32 Hz) frequencies.
Results: There were no group differences in sleep latency by conventionally scored sleep stages ($t = -1.11$, $df=11$, $p = 0.29$). The reliabilities for 4-second scoring of sleep stage (kappa = 0.68, $p < 0.001$) and of artifacted epochs (kappa =0.63, $p< 0.001$) were good. The patients had fewer sleep epochs after sleep onset ($X2 =114$, $df=1$, $p<0.01$) and more artifacts ($X2 = 124$, $df =1$ $p < 0.01$). Patients took longer to attain stable sleep (Breslow = 5.6, $p = 0.02$). The LME model of delta power time series showed group differences ($t=4.9$, $df=2566$, $p<0.0001$), with group:time ($t=4.6$, $df=2566$, $p<0.0001$) and group:time3 ($t=-2.8$, $df=2566$, $p=0.006$) interactions. The model for beta power time series showed group differences ($t=-5.9$, $df=2565$, $p<0.0001$), with group:time2 ($t=-3.9$, $df=2565$, $p=0.0001$) and group:time3 ($t=3.01$, $df=2565$, $p=0.003$) interactions.
Conclusion: The simple method for visually scoring short epochs used in this study enabled reliable scoring of 4-second epochs alongside conventional scoring methods. With this new method, abnormalities in total sleep, total artifacts, and times to stable sleep were found in primary insomnia patients even when their conventional sleep latencies were normal. Parsing the EEG record in short epochs also enabled power spectral time-series models to identify abnormalities in the sleep onset process. These results confirm earlier findings, but suggest dyssynchronies in primary insomnia patients' sleep onset processes across different frequencies. The results encourage studying sleep in short epochs, but also studying the potential biasing effects of removing epochs containing artifacts from insomnia patients' records.

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Prevalence and Consequences of Disturbed Sleep Among Rotating Shift Workers

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Introduction: Shift work research has focused on the effects of rotating schedule on sleep-wake function. These studies have clearly demonstrated disturbed sleep, "daytime" sleepiness, decreased productivity, increased accidents, and impaired mood in shift workers relative to day workers. Therefore, interventions have focused on optimizing shift rotation. Recently, research has shown that there are individual vulnerabilities to sleep disturbance and its consequences. Some individuals consistently have disturbed sleep as a result of circadian, pharmacological, or environmental challenges. An important question is whether the sleep-wake disturbance of shift workers differentially impacts certain individuals. The purpose of this study was to determine whether the consequences of rotating shifts is the direct result of the shift, is mediated by the increased prevalence of insomnia, or an interaction of these two factors.
Methods: A population-based sample of 3283 individuals aged 18-65 was drawn from tri-county metropolitan Detroit (68% response rate; 50.8% Female). Phone interviews were conducted regarding sleep habits, sleep-related disability, medical/psychiatric disorders, and demographics, including shift work status. Individuals reporting rotating shift work (n = 362; mean age = 35.9 ± 12.3; 54% Female) were age and sex matched with day workers randomly selected from the remaining population. Current insomnia was assessed using DSM-IV based criteria and daytime sleepiness using the Epworth Sleepiness Scale (ESS).
Results: Insomnia prevalence was higher among shift workers relative to day workers (15.6% vs. 6.6%; Chi-Square=13.9, $p < .001$). Sleepiness (ESS >13) was comparable between shift workers and day workers (14.4%, 12.7%, respectively; Chi-Square=.4, p=.52). Within day workers there was no significant increase in sleepiness as a function of insomnia (11.5%, 17.4%; Chi-Square=.72, p=.40). However, among shift workers insomnia was associated with a significant increase in the prevalence of sleepiness (12.2%, 30.2%; Chi-Square=11.4, p=.001). Among workers without insomnia, 18.5% have used alcohol, and 25% have used medications for sleep. Of all workers with insomnia, 31% reported using alcohol and 53% reported using medications for sleep. There was no interaction between shift work and insomnia on these parameters. Measures of daytime consequences focused on the frequency of missing social functions, missing housework, or missing work. On all of these questions the frequency of impairment was significantly higher in the insomnia group ($p < .05$ for all). Most importantly, there was a significant interaction between shift and insomnia ($p < .05$ for all). Specifically, this impairment of function was more pronounced in insomniacs working rotating shifts relative to day shifts.
Conclusion: These data confirm shift work is associated with increased prevalence of insomnia. However, only a minority of workers meet DSM-IV criteria for insomnia. Importantly, this minority show the greatest level of impairment. Clearly research is needed to design shifts which minimally impact sleep. However, work needs to focus on identifying those individuals likely to develop shift work sleep disorder, what factors increase vulnerability to the consequences of shift rotations, and how to optimally treat shift work sleep disorder.

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Sleep Misperception: Clinical Characteristics of Over and Under Estimators Among Insomnia Sufferers

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Introduction: Sleep misperception is usually defined as a gross overestimation of sleep-onset latency and wake after sleep onset and an underestimation of total sleep time. Recently, Means, Edinger, Glenn and Fins (2003) have reported that good sleepers and insomnia sufferers cannot be separated by the generic characteristic of underestimation of sleep time and that the perception of sleep may be influenced by personality traits and sleep settings. The objective of the present study is to further document clinical characteristics that may differentiate over/under estimators and good estimators among insomnia sufferers.
Methods: The sample included 109 participants (54% women, mean age = 49 years) complaining of sleep difficulties. All participants underwent a multi-step assessment for insomnia consisting of sleep, psychological, and medical evaluations. Participants met diagnostic criteria for primary chronic insomnia (mean duration of 17 years). They completed daily sleep diaries for an average of two weeks before undergoing three consecutive nights of polysomnographic (PSG) recordings. Sleep diaries were also completed upon arising after each PSG night. Three sleep parameters were targeted for the present study, including sleep-onset latency (SOL), wake after sleep onset (WASO), and total sleep time (TST). Other measures included sleep quality, the Insomnia Severity Index (ISI), and the Beck Depression and Anxiety Inventories.
Results: Difference scores between subjective and objective (PSG) sleep parameters (SOL, WASO, and TST) were first computed for all three nights. Then, difference scores were submitted to a k-means cluster analysis. A four-cluster solution best explained the difference scores variance (R2 = 56.6%). Clusters were respectively labeled: I. good sleep estimators (n = 42), II. WASO under estimators (n = 23), III. SOL over estimators (n = 25) and IV. SOL+WASO over estimators (n = 19). Post-hoc comparisons between these four clusters revealed that over estimators had significantly higher scores on the ISI, and Beck Depression and Anxiety Inventories, compared to good estimators and under estimators. Furthermore, individuals overestimating both SOL and WASO reported more sleepless nights on the diary than individuals in other clusters. On the other hand, there were significantly fewer individuals with mixed insomnia in the under estimators (53%), compared to good estimators (85%) and over estimators (90% for cluster III and 83% for cluster IV).
Conclusion: These results suggest that about 38% of individuals suffering of primary insomnia estimate correctly their sleep difficulties over three consecutive nights while about 40% overestimate either sleep-onset or both sleep-onset and wake after sleep onset. These latter also report more anxiety and depressive symptoms than others do. Furthermore, reporting a high frequency of sleepless nights on the diary may be an indicator of severe sleep misperception. Does sleep misperception in many insomnia sufferers reflect an underlying cognitive schema of misperception in other areas of daily life? Do individuals that over- or underestimate respond differently to insomnia treatment relative to good estimators? These questions remain to be answered.

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Gender Differences in Insomnia are Mediated by Co-morbid Conditions

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Introduction: It is important to determine the degree to which risk factors for insomnia (e.g. gender, medical and psychiatric disease) interact, as well as the mechanisms through which they convey this risk. Shift work, medical and psychiatric disease can be characterized as stressors and women have been shown to have an increased response to a variety of stressors. Thus, we hypothesized that gender differences in insomnia would become more robust with increasing co-morbid conditions (stressors). We further hypothesized that gender differences in insomnia would be greater in symptomatic versus asymptomatic conditions as the former likely carry an additional burden of stress.
Methods: A randomly selected population-based sample of 3283 individuals aged 18-65 was drawn from tri-county metropolitan Detroit (68% response rate; 50.8% Female). Phone interviews were conducted with each individual regarding their sleep habits, medical and psychiatric status, and demographic information. Current insomnia was assessed using DSM-IV based criteria without excluding medical, psychiatric, or shift work. We examined the change in prevalence of insomnia with increasing co-morbid conditions as well as the magnitude of gender differences in insomnia across 15 common medical conditions.
Results: Overall, 11.1% met DSM-IV based criteria for current insomnia (primary or secondary). As expected, there was a significantly greater percentage of women with insomnia when compared to men (13.7% vs. 8.3%, Odds ratio=1.76, 95% C.I.=1.40-2.22). Individuals with medical or psychiatric conditions or shift work were also more likely to have insomnia as compared to those without these factors (13.6% vs. 3.2%, Odds ratio=4.78, 95% C.I.=3.13-7.29). Moreover, there was a clear dose response effect, as the number of co-morbid conditions increased there was a significant increase in the prevalence of insomnia (0=3.2%, 1=4.3%, 2=10.8%, 3=13.8%, 4=21.7%, 5=22.4%, > 6=34.7%; Chi-sq=223.0, $p < .001$). This relationship remained significant even after controlling for age using a partial correlation coefficient ($r = .69$, $p = .03$). Importantly, specific conditions appeared to convey the increased risk of insomnia in women. For example, the highest odds ratio for the risk for insomnia in women was conveyed by neurological disease (epilepsy, stroke, etc; odds=3.09, C.I.=2.22-4.29). In contrast, the female/male ratio was closest to 1 for hypertension and thyroid disorder (odds = 1.2 and .91, respectively; n.s.). Most importantly, in primary insomnia there was no gender difference in the prevalence of insomnia [women (n=25); = 3.3%, men (n = 23); = 3.1%; odds = 1.05, C.I. = .45 - 2.43].
Conclusion: The critical finding of the present study is that in this population-based sample, female gender is not a direct risk for primary insomnia. Consistent with previous research we did find an increased risk of insomnia in women but interestingly, only in individuals with a history of co-morbid medical or psychiatric disorders or shift workers. Moreover, it appears that more symptomatic disorders convey a greater gender risk for insomnia, suggesting that an increased basal response to stress in females interacting in a dose-response manner with the presence of co-morbid conditions may lead to the increased prevalence of insomnia commonly reported in women.

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Prevalence of Sleep Disruption is Increased in Subjects with Diverse Medical Disorders even in Absence of Significant Sleep Complaints

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Introduction: A lack of restorative sleep has been suggested to contribute to the morbidity of many somatic disorders as well as lead to a deterioration of the quality of life in these patients. While the consequences of insomnia in subjects with somatic disorders are a subject of continuing research, there is a paucity of literature assessing sleep disruption in subjects with diverse medical disorders in absence of any sleep complaints. The current study aims to better characterize sleep in various medical disorders in a community-based sample.
Methods: 600 subjects drawn from tri-county area in Southeastern Michigan underwent a computer-assisted random dial survey detailing their sleep habits and presence or absence of any medical disorders, followed by in-laboratory polysomnography with 8.5 hours in bed. Subjects who denied a history of insomnia, defined as a frequent difficulty in initiating or maintaining sleep with interference in daytime activities based on DSM-IV criteria, were assessed for sleep disruption.
Results: Of the subjects who completed the survey as well as in-laboratory testing, 80% (n=429) denied a history of current insomnia (past 4 weeks). Within this group, 74% (n=318) had a history of one or more medical disorders. Subjects with medical disorders were older (44±13 yrs vs. 36±13 yrs, P<0.01) and more likely to be female (55% vs. 43%, P=0.02). To assess the severity of polysomnographically determined sleep disruption within this group of subjects without insomnia symptoms, subjects with specific medical disorders were compared with those without respective disorders. This comparison revealed a lower mean sleep efficiency in subjects with heart disease (n=25, 77% vs. 84%, P<0.01), hypertension (n=115, 80% vs. 85%, P<0.001), diabetes (n=31, 78% vs. 84%, P=0.02), epilepsy (n=11, 74% vs. 84%) and stroke (n=6, 70% vs. 84%, P<0.01) versus those without the respective disorder. However, this difference was not observed in thyroid disorders (n=35, 84% vs. 81%), cancer (n=18, 84%vs 84%), arthritis (n=108, 83% vs. 84%), migraines (n=96, 84% vs. 84%), asthma (n=59, 85% vs. 84%) or emphysema (n=33, 83% vs. 84%). Comparison of the same group of non-insomniac subjects with and without specific disorders also revealed a significantly higher prevalence of sleep disruption (i.e., sleep efficiency below 80%) in subjects with heart disease (48% vs. 25%, P=0.01), hypertension (37% vs. 22%, P=0.001), diabetes (52% vs. 24%, P=0.001), epilepsy (54% vs. 25%, P=0.03) and stroke (67% vs. 25%, P=0.02) but not thyroid disorders (37% vs. 25%, P=0.12), cancer (22% vs. 26%), arthritis (27% vs. 25%), migraines (22% vs. 25%), asthma (27% vs. 26%) or emphysema (36% vs. 25%, P=0.16).
Conclusion: The current study demonstrates a higher prevalence and severity of polysomnographically defined sleep disruption in subjects with medical disorders such as heart disease, hypertension, diabetes, epilepsy and stroke, even in absence of self-reported sleep complaints. Further studies are needed to assess the consequences of asymptomatic sleep disruption in these disease states in an effort to reduce any associated morbidity or mortality.

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Dose Dependent Improvement of Sleep Symptoms Interacts with Gender and Insomnia Subtype

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Introduction: Cognitive-behavioral therapy (CBT) is an efficacious and durable treatment for improving the sleep of patients with insomnia. Little is known about what types of patients will benefit most efficiently from this therapy. If patient factors can be identified that predict who will and will not benefit from CBT for insomnia, treatment efficiency may be improved.
Methods: This study's data were derived from 86 sleep-maintenance insomnia patients enrolled in a study designed to test one-, two-, four-, or eight-session CBT treatment protocols against a no-treatment control. Patients (ages 40-75 yrs., 43 women) were screened via structured interviews, medical examinations, and polysomnography. Those enrolled met criteria for Primary Insomnia and had an average wake time after sleep onset (WASO) > 60 minutes. Baseline assessment included sleep logs, actigraphy (2 weeks each), and multiple questionnaires including the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), the Insomnia Symptom Questionnaire (ISQ), and a sleep-related Self-Efficacy Scale (SES). Baseline questionnaires were used to dichotomize the sample into Type 1 (low self-efficacy & high dysfunctional beliefs about sleep) and Type 2 (higher self-efficacy and low dysfunctional beliefs) subgroups. Patients within each subgroup (Type X Gender) were subsequently assigned at random either to waiting list control or to one of four treatment doses. Doses were administered as follows: one (week 1 only), two (weeks 1 and 5), four (weeks 1, 3, 5 & 7), or eight (weekly) therapist-guided CBT sessions. Each week of treatment they completed sleep logs and actigraphy as well as the ISQ and SES.
Results: Significant differences emerged for total wake time (TWT) derived from actigraphy and subjective insomnia symptoms from the ISQ. For TWT, a significant Dose X Type interaction was found. TWT was significantly reduced for Type 1 subjects receiving a dose of either 1 or 4 treatments; however, for Type 2 subjects significant reductions were found only in those receiving 4 treatments. For the ISQ a significant Dose X Type X Gender interaction was found. The ISQ was significantly reduced for Type 1 females receiving a dose of 1 or 4 treatments; however, for Type 1 males ISQ reductions occurred for those receiving a dose of 2 or 4. For Type 2 females or males, ISQ reductions were observed only for those receiving a dose of 4 treatments.
Conclusion: These results suggest that the optimal dosing for reducing actigraphic TWT and subjective symptoms of insomnia (ISQ) may be 4 treatments over an 8 week period. However, for Type 1 subjects (those with lower self-efficacy and higher dysfunctional beliefs) treatment benefit may occur more efficiently with fewer treatments.

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Comparison of Sleep Parameters by AHI Values in Older Insomniacs

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Introduction: Standards for the classification of sleep-disordered breathing are primarily determined by consensus or convention because there is a lack of sufficient, published data to make evidence-based recommendations. This general observation is particularly true for specific demographic or clinical groups, such as the elderly, where evidence for recommendations is almost nonexistent. In a study of light treatments for older insomniacs, we used a cutoff of ≥ 10 apneas/hypopneas per hour as an exclusion criterion for participation. We were concerned that this cutoff might include participants with substantially different sleep-relevant parameters. The goal of the present study was to determine if our subjects' sleep and associated parameters varied significantly in relation

to their AHI scores.
Methods: Participants Those applicants (N=148, 86 women, mean age 63.5 years ±7.5) considered potentially eligible by a telephone interview that screened for contraindicated medical conditions, medications, and prior sleep disorder diagnoses were evaluated for sleep-disordered breathing using the EdenTraceII® ambulatory monitoring system at home. Parameters obtained were nasal airflow, respiratory impedance, heart rate, snoring severity, body position, and oxygen saturation. The respiratory measures generated data for computation of an apnea/hypopnea index (AHI). Screening was multi-staged: those who met the criterion of <10 AHI were asked to complete 14 days of sleep logs and 7 days of actigraphy and questionnaires. For purposes of analysis we divided the data for the participants who had complete information on self-reported BMI, age, gender, and Epworth Sleepiness Scale (ESS) as well as sleep logs and actigraphic sleep parameters into two groups: those scoring <5 AHI and those scoring between 5 and 10 AHI. We compared the responses of the two groups on all the above measures using unpaired t-tests. We tested whether there were significant differences between subjects scoring below 10 AHI and above the conventional cut-off of 5 AHI, versus those scoring below 5 AHI.
Results: The mean age of the 87 qualifying participants was 63.1 years (±6.9) and 60 were women. There were 66 participants who scored <5 AHI and 21 participants whose scores were ≥ 5 and <10 AHI. Mean values for all subjects on the studied variables were: AHI 3.3 ±2.6; BMI 24.8 ±3.5; and ESS 7.4 ±4.7. Mean Sleep Log findings were: TST 343.0 ±57.1; WASO 77.9 ±56.4; SO 34.7 ±36.4; SE 68.6 ±10.9; TIB 505.6 ±60.2. Mean actigraphy findings were: TST 392.3 ±55.5; WASO 70.6 ±34.1; SO 21.7 ±15.7; SE 78.1 ±7.7. There were no significant differences on these measures for participants whose AHI scores were <5 AHI versus those whose scores were ≥ 5 and <10.
Conclusion: These findings suggest that there was an acceptable level of consistency among our older participants on parameters pertinent to sleep, using the cutoff of <10 AHI for study inclusion. We should note that this consistency might have been influenced by the fact that this was a preponderantly female group of insomniacs screened to be relatively healthy-both psychologically and physiologically-with low BMIs and a moderate level of sleepiness.

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Neuroanatomical Circuitry Involved in Stress-induced Insomnia

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Introduction: Primary insomnia, the most prevalent sleep disorder in the general population, is generally caused by stressful life events. However, little is known about the central pathways underlying the effects of stress on the sleep-wake cycle. It has been proposed that the stability of the sleep-wakefulness cycle depends on reciprocal inhibitory interactions between the ventrolateral preoptic nucleus (VLPO) and wake-promoting areas. Activation of the VLPO is necessary for producing normal sleep, whereas during wakefulness the VLPO is strongly inhibited. Therefore, the increased wakefulness and disrupted sleep observed during insomnia may be caused by decreased activity of the VLPO due to increased stress-induced inhibition. We used acute exposure to a psychological stressor that causes transient insomnia as a simple rodent model to study the basic functional changes elicited by stress on the sleep-wakefulness circuitry.
Methods: Rats were subjected to cage exchange (change to a cage previously occupied by a conspecific) during the light phase (10.00 am). This exposure produces 1 hour of wakefulness followed by 2 hours of normal sleep, and 1-2 hours of reduced sleep and sleep fragmentation (determined in preliminary studies). Control rats were changed to a clean cage. EEG activity was recorded during 2 days before stress exposure (baseline) and continued until rats were killed and perfused 5 and a half hours after cage exchange (90 minutes after the beginning of sleep disturbances). EEG and EMG electrodes were implanted 2 weeks before experiments. Brains were processed for immunohistochemical detection of Fos, a marker of neuronal activity, to analyze what brain regions became activated at the onset of transient insomnia.
Results: Wakefulness during the last hour in stressed rats (48%, n=16) was significantly increased respect to controls (20%; n=4). In the same period, nREM and REM sleep (42% and 9%, respectively) were decreased respect to controls (57% and 22%, respectively). The number of wake and nREM bouts was increased during the 4th hour after cage exchange but not during the last hour, whereas the number of REM bouts was decreased at all time points after cage exchange. Fos expression in stressed rats was decreased in the VLPO and increased in wake-promoting areas (tuberomammillary nucleus and locus coeruleus), in VLPO inhibitory afferents (lateral septum, lateral hypothalamus and dorsomedial hypothalamus), and in stress-sensitive areas that project to VLPO afferents (infralimbic and cingulate cortices, central amygdala and hippocampus).
Conclusion: Exposure to a psychological stressor such as cage exchange induces a period of transient insomnia characterized by increased wakefulness and transitions, and decreased nREM and REM sleep. These sleep disturbances are most likely caused by changes in the neural activity of sleep-promoting (VLPO) and wake-promoting areas, as demonstrated by the pattern of Fos expression observed in insomniac rats. The present results suggest the existence of a neural circuitry that becomes activated at the onset of transient insomnia. This circuit comprises stress-sensitive regions that may affect the activity of VLPO either directly or indirectly via projections to VLPO afferents. Our results also identify possible targets for more specific pharmacological manipulations to alleviate stress-induced insomnia.

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Presence of Underlying Medical Disorders is Associated with more Disrupted Sleep in Subjects with Insomnia

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Introduction: Insomnia is a common symptom among patients seeking treatment at sleep clinics and is associated with adverse social, economic and medical consequences. Presence of diverse medical disorders contributes to the pathogenesis and severity of insomnia. However, which medical disorders are associated with a more pronounced sleep disruption in insomnia patients is currently not known. We sought to study the sleep characteristics in insomnia patients with or without various medical disorders in a community sample to better elucidate the contribution of these disorders to sleep disruption.
Methods: 600 subjects drawn from tri-county area in Southeastern Michigan underwent a computer-assisted random dial survey detailing their sleep habits and presence or absence of any of a set of medical disorders, followed by in-laboratory polysomnography with 8.5 hours in bed. In accordance with the DSM-IV criteria, insomnia was defined as history of frequent difficulty in initiating or maintaining sleep with significant disruption of daytime functioning.
Results: Of the subjects who completed the survey as well as in-laboratory testing, 20% (n=107) met criteria for insomnia. Among the patients with insomnia, 80% (n=86) had a history of one or more medical disor-

ders (the disease group) while the rest 20% (n=27) did not (the no-disease group). The no-disease group insomniacs were younger than the disease-group insomniacs (36±11 yrs vs. 42±12 yrs, P=0.04). There was no significant difference in the gender distribution between the no-disease and the disease groups (52% females vs. 65% females, P=0.3). Within this sample of insomniacs, sleep efficiency was lower in the disease group than the no-disease group (81% vs. 88%, P=0.03). Severity of polysomnographically determined sleep disruption was then compared in insomniacs with each disorder and those without the respective disorder. The mean sleep efficiency was found to be significantly lower in insomniacs with heart disease (n=6, 70% vs. 84%, P<0.01), hypertension (n =26, 76% vs. 86%, P=0.001), arthritis (n=34, 78% vs. 86%, P=0.001), emphysema ((n=14, 72% vs. 85%, P=0.001), and stroke (n=2, 66% vs. 83%, P=0.03) than those without respective disorders. However, differences were not observed in diabetes (n=5, 83% vs. 82%), thyroid disorders (n=13, 80% vs. 83%), cancer (n=7, 81% vs. 83%), migraine (n=33, 82% vs. 83%), asthma (n=25, 85% vs. 83%) or epilepsy (n=4, 81% vs. 83%). The prevalence of significant sleep disruption (defined as sleep efficiency below 80%), was higher in insomniacs with underlying heart disease (67% vs. 28%, P=0.04), hypertension (50% vs. 22%, P<0.01), arthritis (53% vs. 17%, P<0.001), emphysema 71% vs. 24%, P<0.001) and stroke (100% vs. 28%, P=0.03) but not diabetes (40% vs. 30%, P=0.6), cancer (57% vs. 28%, P=0.1), migraines (36% vs. 27%, P=0.3), asthma (32% vs. 29%, P=0.8) or epilepsy (25% vs. 30%, P=0.8).

Conclusion: The present study demonstrates that within insomnia secondary to medical disorders, presence of emphysema, arthritis, hypertension or heart disease is associated with a more pronounced sleep disruption. Further research is needed to understand the mechanisms through which these disorders disrupt sleep.

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Psychological Treatment of Insomnia in Older Adults Using Hypnotics

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Introduction: Several studies have explored the utility of psychological treatments for insomnia in groups that consisted of both persons using hypnotics, and persons not using hypnotics. However, no published study has focused on older adults who are all currently using sleep medications. The current study investigates the efficacy of a psychological treatment of insomnia in a group of older adults using hypnotics.

Methods: To qualify, volunteers had to be using prescription hypnotics at least three times a week for 6 months, and have current insomnia. Baseline PSG was used to screen out other sleep disorders. Forty older adults were randomly assigned to either an active treatment condition that consisted of 8 sessions of a behavioral package including relaxation therapy, stimulus control, and sleep hygiene or to a placebo condition that consisted of a sham biofeedback treatment. Questionnaire data were collected at baseline and post treatment for the following sleep variables: sleep onset latency (SOL), number of awakenings (NWAK), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE). Participants were instructed to maintain baseline levels of hypnotic consumption throughout the treatment period.

Results: To control for differences in baseline values and correlations between baseline and post-treatment measures, post-treatment values were compared with baseline values as co-variables. The differences between groups at post treatment in 3 sleep measures proved significant. For SOL, $F(1,39) = 4.46$, $p < .05$, WASO, $F(1,39) = 4.55$, $p < .05$, and SE, $F(1,39) = 9.86$, $p < .05$, the treated group exhibited better post-treatment sleep than the control group.

Conclusion: The significant improvement in self reported SOL, WASO, and SE suggest that psychological treatment of insomnia may be effective when used in combination with hypnotics in populations of older adults. The use of a placebo control group strengthens our confidence in these results. Clinicians may consider treating hypnotic using insomniacs with behavioral interventions without first weaning patients from medications.

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The Effect of Propranolol on Autonomic Activity and Sleep in Patients with Insomnia

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Introduction: It has been suggested that chronic insomnia might be at least partly due to hyperarousal. Individuals with insomnia have been found to have higher levels of physiological arousal than normal sleepers on a number of variables including heart rate, 24-hour metabolic rate, and EEG frequency. It has also been found that insomniacs have more sympathetic nervous system activity, as measured by heart rate variability, than normals do. These data suggest that a successful treatment for insomnia could focus on reducing the level of physiological arousal insomniacs experience. Therefore, a medication that reduces blood pressure and heart rate, which would be indicative of a drop in sympathetic tone, may improve sleep. The medication that we chose for this was propranolol 40 mg, a beta adrenergic blocking agent.

Methods: We conducted a study of 10 individuals with chronic insomnia as defined by DSM IV criteria. Qualifying participants were studied during three polysomnographic (PSG) evaluations, each one-week apart. The first PSG was for the purposes of screening and for adaptation; it was not included in any analyses. The second and third PSGs were conducted after participants had taken either propranolol 40 mg or placebo before bed for one week. During both weeks, participants also filled out a diary to track subjective sleep quality, mood, and alertness. The PSG included EEG, EOG, EMG, and heart rate variability. A spectral analysis was performed on the heart rate beat to beat intervals in order to determine high frequency (HF) and low frequency (LF) peaks. This corresponds to parasympathetic and sympathetic activity, respectively.

Results: Propranolol did not significantly affect average sleep onset latency (36 minutes for placebo and 23 minutes for drug, respectively, $t = 1.558$, $p = .158$), although the mean values show that participants did fall asleep somewhat quicker on propranolol. Sleep efficiency was not significantly different across the two conditions (75% and 78% for placebo vs. drug, $t = -.657$, $p = .557$). The number of arousals per hour was also similar. Propranolol did not alter subjective measures of sleep quality, mood, or alertness. Autonomic balance showed no difference between conditions (LF/HF = 1.79 vs. 2.14 on placebo vs. drug, $t = -.475$, $p = .655$). These ratios are very similar to previously published data on normal sleepers. However, there was a trend for higher heart rate on placebo vs. drug (68 vs. 63, $t = 1.733$, $p = .127$).

Conclusion: 1) A medication that was expected to decrease sympathetic activity did not improve measures of sleep. 2) Cardiac sympathetic measures were not affected, suggesting that the dose of propranolol used in this study was too low. 3) Our autonomic balance data suggest that the patients in this study may not have been hyperaroused. 4) Hyperarousal is not necessarily associated with a diagnosis of insomnia.

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Coping is Associated with Heart Period Variability in Patients with Insomnia

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Introduction: Stress has been hypothesized to contribute to both the onset and maintenance and primary insomnia, yet little is understood about the mechanisms involved in the stress-sleep relationship in this population. Stress-related increases in autonomic tone, as measured by heart period variability (HPV), may represent one pathway to disturbed sleep in patients with primary insomnia. Previous studies have reported that increases in autonomic tone are associated with arousals during NREM sleep, sleep continuity disruptions and decreases in delta power in both healthy controls and patients with insomnia. Our laboratory has also shown that acute, experimental stress elicits increases in autonomic tone during NREM and REM sleep in healthy controls. In this study, we hypothesized that stress contributes to heightened autonomic tone during NREM sleep in patients with primary insomnia.
Methods: Participants were 24 patients with primary insomnia (mean age = 29.0 years, 67% female). Although lifetime history of depression was not an exclusion criterion, all study participants were free of major depression at the time of study. Subjective stress was measured in conjunction with 3-nights of laboratory sleep studies. Measures included the Perceived Stress Scale (PSS), the Impact of Event Scale (IES) and a measure of event-specific coping style (COPE). The Inventory of Depressive Symptomatology (IDS) and Penn State Worry Questionnaire (PSWQ) were used to evaluate the potential impact of symptoms of depression and trait tendency to worry on the relationship between stress and autonomic tone during NREM sleep. Autonomic tone was measured by autoregressive spectra of interbeat intervals on the EKG (heart period variability) during NREM sleep. The ratio of low-to-high frequency power was used to quantify sympathetic nervous system activity, and normalized high frequency spectral power (.15 - .4 Hz/total power) was used to measure vagal tone. Spearman rank-order correlations were used to evaluate relationships between variables.
Results: Avoidance behaviors and denial as a coping strategy against recent stressful life events were significant predictors of autonomic tone during NREM sleep. Greater use of avoidance behaviors was associated with increased sympathetic activity (rho = 0.69, $p<.01$) and decreased vagal tone (rho = -0.62, $p<.01$). Similarly, increased reliance on denial was associated with increased sympathetic activity (rho = 0.51, $p<.05$) and a trend towards decreased vagal tone (rho = -0.41, $p<.08$). Correlations between symptoms of depression, sympathetic activity and vagal tone were not significant (rhos = 0.38 and -0.37, respectively). Similarly, autonomic tone during NREM sleep was not significantly correlated with ambient stress, intrusive thoughts, or dispositional worry (rho values all < .25).
Conclusion: Responses to recent stressful life events are associated with increases in autonomic tone in patients with insomnia. Results suggest that the use of avoidance behaviors and denial, which have been shown to perpetuate chronic stress, may also play a role in the maintenance of primary insomnia. Results also hint at the relationship between depression, arousal, and insomnia, although the present sample, by definition, did not include patients with current major depression. To the extent that primary insomnia and major depression share symptoms of heightened arousal during sleep, avoidance behaviors and denial may be important correlates of sleep in both disorders.

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Using Chinese Acupuncture Device In Treating Chronic Insomnia

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Introduction: Chronic insomnia affects more than 1 million people in Taiwan. Some patients will search for alternative treatment by themselves with inconsistency effect. Acupuncture is a conventional Chinese medicine that uses physical stimulation in certain point of body to triggers the secretion of certain neurotransmitters. Insomnia was reported to improve by acupuncture in some patients. A small acupuncture device that stimulates three sleep–aid points in the wrist was designed and evaluated the effectiveness of this device in treating the patient of chronic insomnia.
Methods: Patients of chronic insomnia who visit our sleep clinic will be included into this study. All patients will be evaluated by psychiatric and sleep specialists to exclude the disorders other than chronic insomnia. Overnight polysomnography (PSG) will be arranged before and after treatment to exclude the other sleep disorders and evaluate their sleep characteristics. The small Acupuncture device will be used every night 30 minutes before sleep for 8 weeks. Sleep diary will be recorded 1 week before and during the treatment. The insomnia symptoms questionnaire (ISQ), The sleep evaluation questionnaire (SEQ), Epworth sleepiness scale (ESS), Short Form 36 general health questionnaire (SF-36), Beck Depression Inventory (BDI) and State Trait Anxiety Inventory (STAI) will be recorded before and after treatment. SEQ and ISQ will also been recorded every 2 weeks during treatment.
Results: 47 chronic insomniac patients who have the willing to participate were included into this study. 11 patients (2 depression, 1 anxiety, 6 periodic limbs movement syndrome, 2 obstructive sleep apnea syndrome) were excluded after evaluation. 7 (19.4%) patients did not finished the study due to poor response (3), tachycardiac sensation (1), electric shock sensation (1), and others (1 go abroad and 1 did not finish all the questionnaire). 29 patients complete the whole courses of treatment. Their age was 37.7±8.8 years old and 16 (55.2%) patients were female. There are 22 married, 6 unmarried, and one divorced in our patients. After 8 weeks of treatment, the sleep efficiency (78.5% to 86.9%), total sleep time (368 mins to 411 mins), sleep latency (36 mins to 28 mins), total awake time during sleep (33 mins to 10 mins), and their satisfaction of sleep (56% to 69%) recorded by sleep diary were all significantly improved ($p\leq0.05$). The difficulty of getting to sleep and the sleep quality evaluated by ISQ and SEQ were also significantly improved. Depression (BDI) and state anxiety (STAI) in these patients were also improved after treatment. The trait anxiety and the characteristic of sleep evaluated by PSG have no changes after treatment. Body pain, general health, vitality, social function, and mental health were also significantly improved in SF-36. The severity of sleepiness (ESS) was not improved.
Conclusion: Acupuncture has a significant effect in treating the chronic insomnia. It also improves the mental health including the depression and anxiety in patients of insomnia. Further study with control device will be done to exclude the placebo effect.

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Insomnia Safety Behaviors are Predicted by Level of Depression

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Introduction: Harveys cognitive model of insomnia proposes that chronic insomnia can be perpetuated through a reinforcing cycle of dys-

functional beliefs, maladaptive daytime safety behaviours and subsequent further disruption of sleep. Specifically, daytime safety behaviours provide a link between dysfunctional beliefs and ongoing disrupted sleep. Safety behaviours may include plausible coping mechanisms (such as napping or drinking coffee) that are intended to avoid a feared consequence of sleeplessness (such as fatigue). Safety behaviours can therefore contribute directly to poor sleep quality, and can also prevent dysfunctional beliefs about the consequences of insomnia from being challenged. This cognitive model may provide a better theoretical basis for cognitive behavioural therapy for insomnia. Thus, the current study aimed to test the link between self-reported sleep disruption, beliefs about sleep, mood and anxiety, and safety behaviors. Specifically, it was expected that the range and frequency of safety behaviours that a participant engaged in would be predicted by the level of their self-reported sleep disruption, with more severe Insomnia leading to increased range of safety behaviours.

Methods: The sample was comprised of 40 participants (29 women, 10 men, aged 18-33) recruited by advertisement for good and poor sleepers. 13 participants reported chronic insomnia, 14 reported sub-threshold insomnia and 13 reported good sleep using criteria reccomended for the Sleep Impairment Index (SII), and all completed a two-week sleep diary. Participants completed standardized measures of Depression, Anxiety and Stress (DASS), Dysfunctional Beliefs and Attitudes about Sleep (DBAS), and a new measure of safety behaviors, the Safety Behaviours Questionnaire (SBQ) at one time point.

Results: 12 of the 40 participants (30%) reported likely mild or moderate clinical depression using criteria reccomended for the DASS. Regression analysis with SPSS was conducted with predictor variables of (1) ISI (2) DBAS, (3) Depression, (4) Anxiety, (5) Stress, and with the SBQ as the criterion. R for regression was significantly different from zero, $F(5,33) = 6.034$, $p<.001$. Two of the five predictor variables contributed significantly to the regression model and the five variables accounted for 47% (adjusted R2, = 39.2%) of the variance in safety behaviors. Depression accounted for 18.74% of unique variance in safety behaviors; DBAS accounted uniquely for 6.86%, ISI accounted uniquely for 0.47%; anxiety accounted uniquely for 0.24%; and stress accounted uniquely for 0.69%. In addition, there was 20% shared variance. The DBAS and the ISI were not significantly correlated, $r(33) = .22$, $p > .05$.

Conclusion: These results suggest that increased insomnia severity does not lead to increased engagement in sleep-related safety behaviours. Instead, engagement in safety behaviors was better predicted by level of mood in this non-clinical population. Thus, while safety behaviors may contribute to a link between beliefs and attitudes about poor sleep and further sleep disruption, safety behaviours are not unique to those with chronic insomnia. Increased engagement in safety behaviours may be a non specific feature of decreased mood. Further, it was found that some good sleepers held beliefs about sleep that may be considered dysfunctional. The possibility that these features may predispose these individuals to subsequent chronic insomnia needs to be explored.

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Insomnia: Could One Single Element Of The Stimulus Control Package Be Sufficient To Improve Sleep?

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Introduction: Insomnia, a common, individually distressing and economically costly complaint, responds well to multicomponent cognitive behavioural therapy (CBT). However little investigation of single elements of each of the CBT components (e.g. stimulus control, relaxation) has been carried out. In particular, despite stimulus control being a central tenet of CBT and the single intervention with most empirical evidence, whether all of its 5 elements are critical to sleep improvements and whether its mechanism of effect is operant conditioning is unknown. The main aim of this study was to investigate the impact on sleep of a single, situational element deemed to be the core of stimulus control for insomnia. In addition, daily compliance rates with the rule and comments relating to its implementation were gathered and explored.

Methods: Two single cases (A-B design) with volunteers, aged 22 and 25 years, with sleep onset (SOL) and sleep maintenance (WASO) difficulties, were conducted. The rule asked participants 'to get out of bed and do the chosen activity in another room if not asleep within a quarter of an hour'. The data collected via daily sleep diaries during baseline (21 and 22 days) served as a point of comparison to evaluate i) changes in sleep patterns (SOL and WASO) by means of visual inspection of graphic representation and interrupted time series analyses (ITSAs) and ii) therapeutic gains measured as Pittsburgh Sleep Quality Index (PSQI) global score equal or less than 5, SOL and WASO shorter than 31 minutes or reduced by 50%, and sleep efficiency (SE) greater than 85% following treatment implementation (23 days). Individual subject effect sizes were also calculated.

Results: Visual inspection (partially corroborated by ITSAs) indicated that the rule decreased SOL in one (8 nights during baseline as compared to 3 during treatment were in the clinical range) and WASO in both participants (14 nights during baseline as compared to none following treatment for one, and 9 during baseline as compared to 5 following treatment for the other participant were in the clinical range). These changes were clinically significant: SOL and WASO for one and WASO and SE for the other participant returned within the normative range and pre- to post- treatment PSQI scores were reduced by 50%. Effect sizes were small to moderate for SOL and moderate to large for WASO. One participant complied 93 % (12 out of 13) and the other one 54% (6 out of 11) of the nights they were not asleep within 15 minutes.

Conclusion: Despite methodological limitations the findings of this explorative study suggested that additional research is worthwhile: not only clinically significant sleep improvements following an easy to deliver single instruction, requiring thirty minutes to be administered were found but, importantly, it can shed light on the factors underlying stimulus control interventions and the dose-response curve. Participants' comments suggested that a 'distilled component', which epitomised the stimulus control model, might be working by indirectly decreasing cognitive and/or emotional activity rather than by simply 'educating' the individual to associate certain cues with sleep.

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The Perception Of Sleepiness/Alertness Among Insomnia Patients

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Introduction: Patients with Insomnia frequently report experiencing daytime consequences attributed to their sleep difficulties. Consistent with this perception, several reports have indicated that these patients are not only dissatisfied with their sleep but also report lower productivity, decreased memory and higher accident rates. While it is plausible to attribute the daytime consequences of Insomnia to the effects of sleep loss, research in this area has been sparse and results inconsistent. In this context, previous research has shown that 22-28% of patients with Insomnia report symptoms of Excessive Daytime Sleepiness (EDS). However, previous studies have not established the consistency of these findings across different EDS scales. The purpose of this study was to establish the agreement of significant EDS scores in a cohort of Insomnia patients attending a Sleep Medicine consultation using two clinically validated scales.

Methods: Fifty-six consecutive patients (22 male, 34 female; age 42 +/-15) evaluated for chronic insomnia completed the Epworth Sleepiness Scale (ESS) and the EDS scale of the Sleep-Wake Activity Inventory (SWAI) as part of their initial consultation. Patients were grouped as Alert (A) if their ESS and SWAI scores were consistent with no evidence of EDS [ESS score of less than 10 and SWAI score of greater than 50 (N=41)], Sleepy (S) if their ESS and SWAI scores were consistent with EDS [ESS score of >10 and SWAI score of <50 (N=7)] and Mixed (M) if their ESS and SWAI scores were not consistent with each other (N=8).
Results: Twelve patients (21%) were found to have EDS as defined by a score of >10 on the ESS; ten patients (18%) were found to have EDS as defined by a score of <50 on the SWAI. Forty-eight patients were assigned to the Alert or Sleepy groups reflecting a high rate of agreement between the two scales (85%). The groups did not differ in their reported time in bed (A=9.3 +/-2, S=9.6 +/-2, M=9.1 +/-2 hrs) or sleep efficiencies (A=53 +/-27%, S=75 +/-21%, M=47 +/-33%). The groups did differ in their sleep onset latencies with the Sleepy Insomniacs reporting significantly shorter onset to sleep compared to the other groups (A=72 +/-68, S=25 +/-21, M=92 +/-100 min, p <0.04). Consistent with these findings, patients reporting daytime nap behavior were more prevalent among the Sleepy Insomniacs (86%) when compared to the Alert or Mixed Insomniacs (10% and 38% respectively, chi-square p<0.001). Relevant to these reports are the bed-partner ESS scores. Forty-four bed-partner scores (79%) were available and showed consistent findings with the patients scores (A=4.4 +/-4, S=13.8 +/-2, M=8.2+/-4; rho=0.83, p<0.001). Importantly, the frequency of clinical diagnoses (Insomnia secondary to anxiety/psychophysiologic insomnia, mood, or medical condition) did not differ across the groups.
Conclusion: The results of this study showed a high rate of EDS scale agreement in the classification of levels of sleepiness/alertness among Insomnia patients. More importantly, the results showed clinically significant sleepiness, as defined by both the Epworth Sleepiness Scale and the EDS scale of the SWAI, in only 7 patients (13% of the cohort). Future research will be needed to determine the polysomnographic correlates of these findings among those symptomatic of sleepiness and to elucidate the mediating factors of the daytime consequences among the remaining patients.

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The Direct and Indirect Costs Associated with Insomnia

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Introduction: Despite the high prevalence and burden of insomnia, we know very little regarding its economic consequences. Existing cost estimates are derived predominantly from large databases and adopt a retrospective macro approach that lacks sensitivity to individual patterns of health care use and impact of illness. It has been suggested that insomnia sufferers are disproportionate consumers of health care resources, yet direct cost comparisons between good and poor sleepers on these measures have not been conducted. This study undertook a prospective, individual-oriented investigation of the cost consequences of insomnia in the province of Quebec.
Methods: A random sample of 2000 French-speaking adults from the province of Quebec partook in an initial telephone survey as part of a large epidemiological insomnia investigation. Individuals were classified as having no insomnia symptoms, some insomnia symptoms, or insomnia syndrome (DSM-IV diagnostic criteria for insomnia met). Of this sample, 1362 agreed to complete a series of self-administered questionnaires. Data for the first 100 participants in each of the "no symptoms" and "syndrome" groups are reported in this preliminary offshoot study. Insomnia-related costs and overall health-care utilisation costs were estimated by using reported frequency data and unit cost measures derived from provincial health insurance databases.
Results: The proportion of insomnia sufferers reporting any types of consultations with health professionals in the three months preceding questionnaire completion was significantly higher than in sleepers reporting no symptoms (84% vs. 44%, respectively). Other differences between syndrome and no symptoms groups (presented in this order) were found in reported use of prescription medications (63% vs. 40%), absenteeism (29% vs. 14%), reduced productivity (42% vs. 12%), and alcohol use (15% vs. 3%). Reduced work productivity occurred during approximately 9,000 hours in the syndrome group compared to about 2,000 hours in the no symptoms group (three-month reference period). About 41% of individuals in the syndrome group were taking medication for insomnia, anxiety or depression, either alone or in combination, compared to 7% of the no symptoms group, with total prescription medication costs for the three-month period totalling $12,528 for insomnia syndrome and $6,938 for good sleepers. Using the 14% prevalence rate identified in this study, 3-month expenditures on insomnia, anxiety and depression medication by individuals with insomnia syndrome in the province of Quebec are estimated at approximately $6 million, $16.7 million, and $15.3 million, respectively. (All group differences were significant at a minimum of p. < .05)
Conclusion: Insomnia sufferers report more health-care consultations, prescription medication use, alcohol use (sleep aid), absenteeism and lost productivity than sleepers with no insomnia symptoms. In particular, insomniacs report more than four times more hours of reduced work productivity than good sleepers. In the province of Quebec, the cost of prescription medications purchased to treat individuals with insomnia syndrome is estimated at approximately 24.5 million, annually. This figure is likely a gross underestimate of insomnia medication costs, as many individuals who do not meet strict DSM-IV criteria nonetheless take prescription products.

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Case Control Study of Insomnia in the Elderly

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Introduction: Insomnia is common among the elderly. Its management requires delineation of multiple causative factors. Standardized evaluations are not well established, although a variety of approaches have been proposed. Controversies remain about the relative diagnostic roles of actigraphy, polysomnography, physiological markers of circadian phase and amplitude, and subjective reports of difficulty initiating or maintaining sleep. The nature of functional, sleepiness, and QoL deficits among those reporting insomnia requires better understanding to address symptoms perceived by patients as important to their well-being. Sleep-wake regulation changes may potentate insomnia risk arising from conditions associated with sleep interruption including somatic disorders, sleep disorders, and psychological or psychosocial stressors. Alternatively, changes in the restorative capacity of sleep may contribute to insomnia perception and its consequences. Thus, we performed a case-control study of elderly individuals in order to investigate the multifactorial origins and consequences of insomnia utilizing multiple subjective and objective measures for defining insomnia and its consequences.
Methods: Nondepressed, cognitively intact, community residing, elderly individuals were screened for insomnia using standardized criteria. Cases indicated current frequent (3-7 nights/week) troubles "either

falling asleep, staying asleep, or waking up too early (insomnia)" that were present for >3wks. Controls indicated never having these troubles in the past 12 months; or rarely so but not over the past 3 weeks. Secondary analyses incorporated objectively determined sleep efficiency into group definitions. Groups were compared on the basis of demographics; PSG; at-home wrist actigraphy; MSLT; comprehensive nueurobehavial and psychological assessment batteries; generic and disease specific health-related QoL indices; co-morbidity and somatic symptom assessments; and medication use.

Results: 100 cases and controls are being compared (mean age (SD) 71.4 (4.6) vs. 72.7 (5.5) yrs; 33% and 40% males, respectively). Cases reported substantially worse sleep quality based on multiple self-report indices (e.g., PSQI and diary reports, $p<0.0001$). In contrast, differences in objective measures of sleep times, awakenings, and sleep efficiency were modest or absent; e.g., mean total sleep time when measured by actigraphy did not vary between groups. A notable exception was mean in-lab sleep efficiency (71.7% for cases vs. 76.5% for controls, $p=0.009$). Generally, cases did not have greater daytime sleepiness or reduced performance by objective measures (e.g., median MSLT was 11.3 among cases vs. 10.2 min among controls; $p=0.003$). In contrast, numerous large and significant reductions in subjectively reported QoL and performance (SF-36, FOSQ, AD-ACL, POMS, etc) emerged as did a few specific psychological and co-morbidity group differences.

Conclusion: There are large group differences in many subjective measures of sleep time and quality but few differences in objective measures. Important differences in subjective measures of sleepiness and QoL emerged that were not reflected in objective measures. Physiological changes, medical conditions, and psychological conditions may play roles in specific individuals. Results are consistent with the notion that insomnia may result from problems with some restorative aspect of sleep that is not fully reflected in differences in actual sleep amounts.

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What Aspects Of Cognitive-Behavioral Therapy For Insomnia Do Patients Find Helpful?

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Introduction: Research consistently shows that cognitive-behavioral therapy (CBT) is an effective treatment for insomnia. Less is known however, about consumer satisfaction and what therapeutic elements patients find helpful. The present study reports how patients who completed group CBT for insomnia rated the different components of treatment.

Methods: Participants were 94 outpatients who completed the Insomnia Program at the Stanford Sleep Disorders Clinic and filled the relevant questionnaire. Participants presented with a chief complaint of insomnia and many had co-morbid psychiatric, sleep, or medical disorders. Use of patient data was approved by the Institutional Human Subjects Review Board in compliance with HIPAA regulations. Treatment consisted of seven group sessions (1.5 hours) and included education about sleep and sleep hygiene, stimulus control, sleep restriction, breathing relaxation, and cognitive restructuring. The main measure used in this study was a questionnaire that lists 26 therapeutic elements and asked patients to rank each on how helpful it was, using a Likert Scale (0 indicated that a treatment element was either not helpful or not applicable; 1, 2, and 3 indicated the element was slightly, somewhat, or very helpful, respectively.)

Results: The results are organized by four conceptual therapeutic elements (sleep education (5 items, mean 1.26±0.64), behavioral components (6 items, mean 1.64±0.64), cognitive components (4 items, mean 1.91±0.90), and non-specific therapeutic elements (6 items, mean 1.75±0.84). Whereas general education about sleep was rated very high (2.46±0.78), other common sleep hygiene components (reducing caffeine or alcohol, exercising, not napping, and turning around the clock) had rather low ratings (0.84 to 1.37). Of the behavioral components, breathing relaxation, keeping the same wake-up time, and sleep restriction had the highest rankings (1.98±1.02, 1.95±1.04, and 1.82±1.07). Getting out of bed when can't sleep, finding pleasurable things to do when unable to sleep, and eliminating non-sleep activities from the bed and bedroom had lower ratings (1.28 to 1.67). The four statements pertaining to changing cognition received very high ratings. These included "Not trying to force sleep" (2.15±0.97), "Accepting that sleep may not be forced" (1.88±1.20), "Accepting that I may not get as much sleep" (1.76±1.16), and "Learning that I can trust my own sleep system" (1.59±1.11). Nonspecific therapeutic factors have also received very high ratings. These included "Receiving input from group members" (1.73±1.10), "Feeling that my problem is taken seriously" (1.97±1.13), "Learning from group discussions" (2.18±0.88), and "Feeling hopeful that my insomnia will improve" (1.86±1.10). Of the remaining therapeutic elements, monitoring sleep in daily sleep diaries also had a high rating (1.98±0.97).

Conclusion: The results suggest that the therapeutic milieu, which has received little attention in the past, might be an important aspect of insomnia treatment. The results also indicated that patients identified the cognitive components, reflecting acceptance and reduced need to control sleep as the most helpful elements of the insomnia treatment. Whereas sleep education and behavior changes are the most commonly used and most researched non-pharmacologic treatment components, the present study suggests that attention needs to be also paid to changing cognitions about sleep and to non-specific therapeutic elements.

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Awakenings: Do Patients With Primary Insomnia Differ In Number Or Duration Of Awakenings Or In The Stages From Which Awakenings Occur As Compared To Good Sleeper Controls?

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Introduction: Patients with sleep maintenance insomnia report that they experience increased wakefulness after sleep onset. When assessed with polysomnography (PSG), such patients are reliably found to exhibit increased wake after sleep onset time (WASO) as compared to good sleeper controls. Not clear from prior research is whether the increase in WASO corresponds to longer bouts of wakefulness or a greater incidence of awakenings. Also unclear is whether patients with insomnia wake up from different stages of sleep than do good sleepers. In the present study, these factors were evaluated in two samples of subjects.

Methods: Two groups were evaluated: Primary Insomnia (PI, n = 18) and Good Sleeper controls (GS, n = 16). All the PI subjects had a complaint of sleep maintenance insomnia. Chi-Square and t-tests revealed no differences between groups for sex (GS: 66% female, PI: 72% female, $\chi 2 = .13$, $p < .72$), age (GS: 37.8 yrs (10.6); PI: 39.9 yrs, (11.5); $F = .33$, $p < .57$) or BMI (GS: 24.3 (2.8), PI: 24.6 (2.3); $F = .11$, $p < .74$). All records were scored in 30-sec epochs according to Rechtschaffen and Kales criteria. In addition to assessing the normal sleep continuity and architectural variables, number of awakenings (> 15 seconds), average duration of awakenings, and proximal sleep stages (stage of sleep which

immediately preceded the awakenings) were evaluated for group differences. T-tests were calculated to examine differences between the groups on number of awakenings and length of awakenings. Mixed model ANOVAs (2 * 6 [Group * Stages]) were used to assess whether the groups awoke from different stages. The stage data were arrayed as percents (percent of awakenings per subject arising from Stages 1,2,3,4,REM or MT).
Results: PI subjects awakened more frequently (21.6 vs 14.3, $F = 4.3$, $p < 0.05$) but the average duration of awakenings were comparable. The Mixed-model ANOVAs revealed that the two groups awaken from Stages 1,3,4 and MT with similar frequency but that the PIs awakened significantly more often from REM Sleep (16% vs 9%, $p < 0.01$) and Stage 2 sleep (39% vs 23%).
Conclusion: The results from this preliminary study are suggestive. The finding that the PIs woke more frequently is consistent with their presenting complaint and accounts for the increase in PSG measured WASO. The comparable duration of the awakenings (along with the increase in frequency) suggests that the patients in this sample did not have significant problems with "re-initiating" sleep. Thus, as the term sleep maintenance insomnia implies, the problem in patients with middle and late insomnia may be precisely related to the aberrant occurrence of awakenings. The increased proportion of awakenings from the more activated stages of sleep is consistent with this conceptualization. That is, patients with middle and late insomnia may be more vulnerable to awakenings from the stages of sleep that are more cortically activated.

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Source Localization of Abnormal Cyclic Alternating Pattern in Fibromyalgia Patients with Non-Restorative Sleep

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Introduction: We have previously described a primary frequent periodic EEG arousal phenomenon during nonREM sleep comprised of clusters of high amplitude delta waves, with overlapping alpha, beta and theta frequencies in fibromyalgia patients with non-restorative sleep, daytime fatigue, and diffuse myalgia(1). This sleep-related periodic EEG pattern is a high frequency variant of cyclic alternating pattern (CAP) (2,3). We hypothesized that low-resolution electromagnetic tomography (LORETA) would determine the cortical spatio-temporal genesis of the CAP sleep anomaly(4).
Methods: Two female subjects (aged 25 & 57 years) with nonrestorative sleep and fibromyalgia symptoms who were found to have abnormal frequent CAP, but no other sleep anomaly on a previous standard sleep recording, and free of all medications for at least 2 weeks, participated in a second overnight sleep recording that employed a 19-lead EEG, right & left occulogram, and submental EMG. The sleep studies were staged according to standard criteria. Serial repeated B-phase pre-CAP samples (3-seconds) and corresponding A-phase CAP samples were taken from non-REM sleep across each record. Cross-spectral analysis was performed for beta, alpha, theta and delta frequency domains. For each frequency domain, the global 3-D distribution of current density was calculated with LORETA for cortical gray matter and hippocampus. The voxel-by-voxel t-values were compared, and maximal current densities were visualized using the Talairach human brain atlas, with a spatial resolution of 2-7 mm3.
Results: The most prominent increases in current density that occurred during an abnormal A phase of the CAP event were in the delta, theta and alpha bands. Maximal increases for delta (4066%) and theta (713%) occurred in the medial frontal gyrus. The maximal increase in the alpha band (820%) occurred in the middle temporal gyrus.
Conclusion: The LORETA method permitted 19 lead EEG source localization of the A phase component of frequent abnormal delta, theta and alpha multi-frequency CAP-like bursts to originate in the medial frontal and middle temporal areas of the cortex. These source localization regions of the brain advance our understanding of the contribution of frequent polyphasic CAP to unrefreshing sleep in a subgroup of patients with fibromyalgia.

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Sustained Endocrine and Sleep Responses to a Psychological Stressor in Primary Insomnia

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Introduction: An important characteristic of the sleep disturbance in primary insomnia (PI) is its persistence after resolution of an inciting disturbance. One potential mechanism to explain this clinical feature is delayed recovery of central arousal systems important to insomnia pathogenesis after stress. In support of this, several studies have demonstrated that patients with primary insomnia (PI) have moderate hyperactivity of the HPA axis. We previously reported the utilization of a standardized psychological stressor (the Trier test) to study the dynamics of endocrine stress responses in PI. We now describe the effects of this protocol on objective and subjective measures of nocturnal sleep.
Methods: 15 patients with a complaint of insomnia lasting at least one year (mean age = 32.2; 7f) were compared to twelve controls (mean age = 31.2; 5f) in a "background" laboratory protocol examining nocturnal sleep, daytime alertness (MSLT), and hormonal measures. This protocol differed from that reported previously by including a fourth nPSG recording to assess recovery effects. On the third evening, subjects were approached about a second, nested protocol in which a public speaking task would be required the following morning ("bracketed" Trier test). For those who consented (12 of 15 with insomnia; 12 of 12 with normal sleep), time was provided that evening for topic selection and speech preparation. The following morning, subjects spoke before an audience of research assistants and psychology interns. After completion of the task, the background protocol resumed with MSLT and hormonal measures, and a fourth PSG recording. Urine was collected throughout the study in 8-hour aliquots for measurement of cortisol and catecholamines. Sleep and MSLT measures were assessed with repeated measures general linear models. Increments in hormonal indices were assessed with two-sample t-tests (Systat, SPSS.)
Results: Consistent with the previous study, PI subjects and controls had statistically indistinguishable 24-hour levels of urinary free cortisol (CORT), norepinephrine (NE), and epinephrine (EPI) at baseline. During the 8-hours after consenting to the speech protocol and receiving instruction, PI subjects showed a substantially greater increment in NE excretion relative to comparable samples on day 2 (43% vs 0%), that persisted through the following night. Average MSLT values were slightly elevated in PI subjects, but there was no significant effect of group or day. Objective measures of nocturnal sleep disruption (sleep latency, sleep efficiency, and NREM stage 1 percent) showed robust increments for both controls and PI subjects the night before the speech ($p < .02$ for all measures). In contrast to normal subjects, whose sleep showed complete normalization on night 4, PI subjects showed persistent sleep disruption comparable to that on night 3 ($p < .03$ for sleep efficiency). Subjective measures of sleep quality showed significant effects of group and day, but no interaction.
Conclusion: PI subjects show persistence of objective sleep disruption for at least one night after exposure to an acute psychological stressor. This is distinct from normal subjects who, after completion of the public speaking task, resume normal sleep. PI patients also show persistent elevation in urinary catecholamines over the same time period. These

findings are consistent with the hypothesis that PI is characterized by delayed normalization of central stress responses after perturbation by a stressor, and that this delay is important in the pathology of PI. This study also establishes the utility of the "bracketed" Trier test as a paradigm for inducing robust sleep disruption in both PI subjects and normal controls.

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Frequency of Sleep Apnea in Patients with Primary Insomnia

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Introduction: The association of insomnia and sleep related breathing disorders (SRBD) was first recognized 3 decades ago. In 1973 the sleep apnea syndrome was described through systematic monitoring of respiratory parameters during all night recordings. Surprisingly, this finding has not been well integrated in routine investigation of insomnia. Currently, the practice parameters for evaluation of insomnia indicate that polysomnography are not routinely used to screen patients with insomnia complaints. In contrast to previous studies, which evaluate the frequency of insomnia in SRBD patients, our purpose was to evaluate the frequency of obstructive sleep apnea in subjects with primary insomnia.
Methods: 55 patients successively referred to the sleep clinic with complaint of primary insomnia (more than 30 min to fall sleep or more than 30 min to fall back sleep for at least 3 nights a week for the last 6 months) was evaluated with clinical interview, sleep history and review of system. Based on this evaluation, these patients were considered primary insomniacs and underwent a portable polysomnographic study. The polysomnogram included the following parameters: respiratory effort with piezo bands, nasal airflow measured with nasal pressure transducer, oral airflow measured by thermistor, microphone and nocturnal oximetry.
Results: The fifty-five patients (23 males, 32 females, mean age 52., mean RDI 6.7 events/hour) had the following insomnia complaints: 17 (30.9%) had sleep maintenance insomnia, 10 (18.2%) had sleep onset insomnia while 28 (50.9%) had both types. 26 (47.3%) out of 55 patients had RDI > 5 events/hour. Of these 26 subjects, 4 patients had sleep onset insomnia, 9 patients had sleep maintenance and 13 patients had both conditions. There was no significant difference in the frequency of Obstructive Sleep Apnea (OSA) between types of complaints.
Conclusion: Patients with insomnia frequently present SRBD, as indicated in earlier studies. A causal relationship is not yet established. It is known that breathing problems cause sleep fragmentation, but the complaints of problems falling asleep and falling back to sleep after awakening are also frequent in SRBD. It is not known whether difficulty maintaining sleep develops after SRBD is present or the progression of SRBD contributes to the maintenance of insomnia complaints. Patients with sleep onset and sleep maintenance insomnia had similar rates of SRBD in this study. We suggest that with the initial evaluation of patients with sleep onset and sleep maintenance insomnia it is important to routinely screen for the presence of SRBD. Further studies are necessary to understand the pathophysiology and progression of sleep apnea insomnia syndrome.

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Prevalence and Correlates of Physiological Hyper-arousal in Patients with Primary Insomnia

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Introduction: The physiological hyper-arousal of primary insomnia (PI) is reflected in increased activity of the autonomic nervous system and increased sleep latency on the multiple sleep latency test (MSLT) despite nocturnal sleep disruption. The clinical diagnosis of primary insomnia is currently one of exclusion, however, because the diagnostic utility of these distinguishing features has not been assessed. As a first step in this process, we evaluated the comparative distribution of indices of autonomic function, hyper-arousal, and objective sleep disruption in comparable populations of subjects with PI and normal controls.
Methods: 53 patients with a complaint of insomnia lasting at least one year and having no evidence of medical or psychiatric disease on examination (primary insomnia, PI; mean age = 34.3, range = 20-55; 29f), were compared to 58 controls (mean age = 33.7, range =18-58; 29f) in a standardized 24-hour laboratory evaluation. Nocturnal PSG (including screen for apnea and PLMS) and daytime MSLT recordings were performed. Urine was collected in 8-hour aliquots for determination of catecholamines, cortisol and creatinine. Multiple questionnaire assessments were performed, including Hamilton depression scale, FIRST stress assessment, POMS, PSQI, BDI and the Epworth Sleepiness Scale.
Results: We operationalized the definition of PI with physiological hyperarousal (PIhyper) as that subset of subjects reporting insomnia who showed sleep efficiency below the median on PSG (first night in laboratory), and mean MSLT greater than the population median the following day. 19 of the 53 insomnia subjects met these criteria. Comparing these subjects to the other insomnia subjects, PIhyper were slightly older (37.2 vs 33.8y) and more likely to be male (63.2% vs 35.5%) than the rest of the insomnia population. Baseline 24-hour urinary cortisol, epinephrine, and norepinephrine were all higher in the PIhyper subjects than in either of the other two populations, but these differences were not statistically significant. Among questionnaire instruments, the Hamilton, PSQI and FIRST all showed significant variation with group (ANOVA; $p<.001$), and average values were highest in the PIhyper group for all three. Only the Hamilton Depression scale meaningfully distinguished between insomnia and PIhyper (Bonferroni, $p<.05$). (The maximum score on the Hamilton for any subject was 6.)
Conclusion: Prospective identification of primary insomnia patients who exhibit physiological hyperarousal may be important to studies of the consequences of insomnia, and to their clinical management. Evidence that these subjects have increased SNS and HPA activation suggests that the pathological implications for this subset of insomnia patients may be distinct. While subjects with PI and hyperarousal on PSG/MSLT show increased levels of catecholamines and cortisol, these are not sufficiently elevated as to be useful prospectively. Questionaire instruments, particularly the Hamilton Depression scale, seem to provide greater potential diagnostic utility.

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The Role of Chronic Pain on Sleep

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Introduction: Individuals suffering of chronic painful physical condition (CPPC) often have concomitant sleep disturbances. In pain clinics,

as many as 90% of patients reported at least one sleep disturbance. The intensity of sleep disturbances has been also correlated with greater pain, depression and disability. While the majority of clinical studies concentrated mostly on a specific type of chronic pain and targeted mainly patients with pain, community-based surveys assessed associations between sleep disturbances and pain in a broad manner. Therefore, little information is available about how chronic pain is related to sleep disturbances in the general population.

Methods: 18,980 participants aged 15 years or older from five European countries (United Kingdom, Germany, Italy, Portugal and Spain) and representative of approximately 206 millions Europeans were interviewed by telephone. The interview included questions about sleeping habits, health, sleep and mental disorders. CPPCs were obtained through questions about medical treatment, consultations and/or hospitalizations for medical reasons and a list of 42 diseases. Insomnia symptoms were defined as difficulty initiating (DIS) or maintaining sleep or non-restorative sleep (NRS) lasting at least one month and accompanied of at least mild daytime consequences.

Results: At least one CPPC was reported by 17.1% of the sample. More than 40% of individuals with insomnia symptoms reported at least one CPPC. CPPC was associated with more frequent difficulty or inability of resuming sleep once awake and a shorter sleep duration. Insomnia subjects with CPPC complained more frequently of anxious or depressed mood, irritability and fatigue than did the insomnia subjects without pain. In multivariate models, CPPC, especially backaches and joint/articular diseases were at least as importantly associated to insomnia then were mood disorders with odds ratios ranging from 4.1 to 5.0 for backaches and from 3.0 to 4.8 for joint/articular diseases.

Conclusion: Our results show that chronic pain is frequent among subject with insomnia: more than 40% of them reported at least one chronic painful physical condition. Chronic pain can be a factor that contributes to the chronicity of insomnia. CPPC is associated with a worsening of insomnia in several aspects: the presence of pain increased linearly with the number of insomnia symptoms; compared to subjects who have insomnia without pain, those with a chronic painful physical condition suffered of insomnia for a longer period and experienced more daytime consequences of insomnia.

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Lack of Effect of Propranolol on Sleep Bruxism: a Controlled Double-Blind Study

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Introduction: Tooth grinding/sleep bruxism (SB) is reported by approximately 8% of the adult population. A case study reported a reduction of the number of masseter muscles contractions with propranolol, a beta-adrenergic blocker (Sjoholm, 1996). Another study also reported a reduction in tooth-grinding with propranolol in patients with neurologic disorders (Amir, 1997). The aim of this study was to assess, in a controlled double-blind study, the effect of propranolol on SB.
Methods: 8 SB subjects were selected according to tooth-grinding history (>3 nights/week) and one night of polysomnographic recording for SB diagnosis. The SB diagnostic night, also used to rule out other sleep disorders (e.g., sleep apnea syndrome, periodic limb movements), was recorded following a habituation night. Sleep and SB were recorded with the Harmonie software (Stellate, Canada). The age of SB patients was between 20 and 28 years old (5w, 5m). Polysomnographic recordings of 2 experimental nights, one with placebo and one with propranolol (long-acting, 120 mg), were separated by 1 washout week according to a random order. Sleep scoring (Rechtschaffen and Kales, 1968) and oromotor/SB (Lavigne, 1996) were analysed with validated criteria. Heart rate variability (HRV) - i.e., low frequency (LF) [0.05-0.15Hz] and high frequency (HF) [0.15-0.4Hz] - was calculated with a Power Welch spectral analysis using a customised MatLab (USA) application. The HF was used as an index of the parasympathetic activity whereas the LF/HF was used as an index of the sympathetic activity. Differences in HRV between placebo and propranolol nights were assessed using 3-minute sections in the absence of muscle (e.g., motor) activity for all subjects during sleep stages 2, 3&4 and REM. Statistical analyses were done with ANOVA and t-tests.
Results: Overall, no statistical differences between propranolol and placebo nights were observed for sleep and oromotor/SB variables (p>0,07). Amongst the variables observed: the mean ± SEM sleep efficacy under placebo and under propranolol was 92.7 ± 2.3% and 92.0 ± 2.3%, respectively; the micro-arousal index was 9.5 ± 1.7/hr and 10.6 ± 2.2/hr, respectively; the SB index was 5.4/hr and 6.5/hr, respectively. No difference was observed for other variables, such as sleep stage distribution, masticatory muscle tone and parasympathetic (normalized HF) tone. However, propranolol increased the mean RR intervals of 8% measured over night, indicating a decreased mean heart rate (p=0.019) and lower sympathetic tone (p=0.025).
Conclusion: Propranolol, a beta-adrenergic blocker, decreased the mean heart rate and the sympathetic tone but did not influence any of the sleep and SB variables over the night. Propranolol is thought to be both a centrally and peripherically acting medication while SB is described as being centrally controlled (Lobbezoo F.,2001). We are currently assessing the effects of a "centrally" acting alpha-agonist, clonidine, on SB.

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Treating Parasomnias with Hypnosis

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Introduction: This study is an attempt to replicate Hurwitz et al (J. Ment. Nerv. Disease, 1991, pp. 228-233) concerning their hypnotic treatment of sleepwalking and sleep terrors.
Methods: Studied were 39 patients (17 females), mean age 32 (range 6-71), referred between 1994 and 2000 for treatment of severe and chronic parasomnias. Twenty patients had developed their parasomnias before age 10. Each patient was evaluated by a Mayo sleep specialist. In 24 of the 39 patients, a PSG was done with extended EEG montage, read by a neurologist. The PSGs of those referred for hypnotic treatment were all WNL concerning EEG, respiration, and PLMs. Final diagnoses were 12 Sleepwalking, 11 Nightmares, 6 Sleep Terrors, and 10 "Other" (Epic Dreaming, Sleep Moaning, etc.) Treatment usually consisted of one 60 minutes session. (Nine required a second hypnotic session). After reviewing the patient's history and knowledge of hypnosis, PJH introduced a trance with the methods of eye fixation, deepening staircase, and drifting in a cloud. Patients were asked to go along with these suggestions even if they did not feel hypnotized. All complied. All were then asked to imagine a movie of themselves showing a normal night's sleep without any parasomnia. This was fortified by suggestions that their parasomnia could now be abandoned because they no longer served a useful purpose. Testing at the end of the hypnotic session revealed that 6 patients were not hypnotized. Patients then received a tape of their hypnotic session and listened to it daily for three weeks, with a taper thereafter.
Results: Patients were sent a 1 page questionnaire after 1 month, 1.5 years, and 5 years. On the one month follow-up, 26 patients responded (66%). Fourteen rated themselves as much or very much improved, 12 as minimally or not improved. Nine (35%) had had no spells whatsoever during that first month. The eighteen month follow-up was sent only to the 26 who had responded at one month. There were 20 replies. Ten still felt "much" or "very much" improved. Of the ten, seven felt that their improvement was due to hypnosis, three listed drugs or time as major improvement factors. Only 17 patients of the original 39 were available for the five year follow-up. Seven responded (response rate 41%). Six of them felt "much" or "very much" improved, one did not. Five attributed their improvement to hypnosis.
Conclusion: The study is flawed by the lack of a control group. Nevertheless, the first month response of 35% with no events whatsoever seems impressive in this group of severe and chronic parasomniacs. Also, half of the respondents (25% of the original sample) still felt much improved 18 months after hypnosis, and six patients still felt much improved five years after the one hour treatment, suggesting that in some patients the effects may be long lasting. In sum, this study suggests that a one-hour hypnosis session may be a cost-effective first treatment for many parasomnias.

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Comparison Between Right and Left Masseter Muscle Activity in Sleep Bruxism Patients

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Introduction: Sleep bruxism (SB) is a stereotyped movement disorder that involves bilateral activation of jaw closure muscles (e.g., masseter and temporal). This study was performed to compare masseter activity on right and left sides in SB subjects since portable devices usually record muscle activity on one side only.
Methods: Data from 15 SB subjects were included in this retrospective study. The first night was for habituation. Polysomnographic recordings performed on the 2nd night included EEG, EMG (left and right masseter, temporalis, anterior tibialis and digastric), audio and video monitoring. SB was scored visually from left and right masseter EMG signal. Video

recordings were used to discriminate SB from other activities involving oromandibular movement. One trained observer performed all the scorings and the selected bursts (more than 6600 bursts on each side) were saved into data files. Three types of SB episodes were scored: phasic (3 EMG bursts lasting 0.25-2.0 seconds), tonic (EMG bursts lasting more than 2.0 seconds) and mixed (both types within an interval of 3.0 seconds). Episodes were separated by intervals of more than 3 seconds. The following variables were evaluated on each side for each subject: number of SB episodes, mean number of SB bursts/episode, mean burst duration/episode (seconds), mean RMS burst amplitude/episode (μV) and total RMS burst amplitude/episode (μV). Values obtained from the right and left sides were compared using the Bland and Altman limits of agreement. The first step to obtain these limits was to calculate the difference between the values from the left and right side (left - right) for each subject. The mean difference and the standard deviation (sd) of the differences were then estimated. It can be expected that 95% of differences between sides will lie between the mean difference ± 2sd. These are the limits of agreement. They can be compared to the average value from both sides (overall mean) for a clinical appreciation of the lack of agreement.

Results: The following overall mean ± SEM and limits of agreement were obtained: - number of SB episodes: mean 61.9 ± 6.5, limits -1.5 and 1.5. Thus, the left side may have 1.5 episodes below or 1.5 episodes above the number of SB episodes on the right side, - mean number of SB bursts/episode: mean 7.0 ± 0.4, limits -0.28 and 0.31, - mean burst duration/episode: mean 1.4 ± 0.1 seconds, limits -0.26 and 0.21, - mean RMS burst amplitude/episode: mean 33.6 ± 2.3 μV, limits -14.5 and 13.6, - total RMS burst amplitude/episode: mean 250.5 ± 26.3 μV, limits -106.2 and 111.0.

Conclusion: The comparison between the overall mean and the limits of agreement reveals that the agreement between values obtained from masseter muscles on both sides was excellent, at the exception of variables which imply the amplitude. This study shows that the evaluation of SB frequency and duration can be based on unilateral masseter muscle scoring when done in conjunction with video recording.

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Post-Arousal EEG Activity During Sleepwalking Episode

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Introduction: Sleepwalking is considered a disorder of arousal in which there occurs a physiological dysfunction in the neural regulation of generalized cortical activation. Early studies found that EEG recordings during somnambulistic episodes were characterized by a combination of alpha, theta, and delta frequencies, without evidence of clear wakefulness. Schenck et al. (1998) identified three post-arousal EEG patterns following arousals from slow wave sleep (SWS) in adults with sleepwalking and sleep terrors. Our group recently showed that sleep deprivation significantly increases the frequency of somnambulistic episodes recorded in the laboratory. The goal of the present study was to evaluate the distribution of the post-arousal EEG patterns associated with sleepwalking episodes observed in the laboratory at baseline and following 38 hours of sleep deprivation.

Methods: Ten sleepwalkers (3 males, 7 females, mean age: 25.1; SD: 4.09) were investigated in the sleep laboratory. All participants underwent a screening night prior to the study. They were then monitored during a baseline night (BN) and a recovery night (RN) following 38 hours of sleep deprivation. The two conditions were counterbalanced. The post-arousal EEG activity was categorized according to the three patterns identified by Schenck et al. (1998): I) diffuse rhythmic and synchronous delta activity, most prominent in bilateral anterior regions, II) diffuse and irregular moderate-to-high voltage delta and theta activity intermixed with alpha and beta activity, and III) prominent alpha and beta activity, at times intermixed with moderate voltage theta activity. EEG tracings were assessed over the duration of each sleepwalking episode.

Results: Five behavioural episodes were recorded from SWS at BN and 30 during the RN. Movement artefacts prevented the detection of clear EEG patterns in 7 of the 35 (20%) SWS episodes (1 from BN and 6 from RN). There was no significant difference in the distribution of post-arousal EEG patterns identified during BN and RN. The distribution of post-arousal patterns during sleepwalking episodes was: pattern I (2.9%), pattern II (22.9%), pattern III (31.4%), a combination of patterns I and II (8.6%), a combination of patterns I and III (8.6%), and a combination of patterns II and III (5.7%). Two episodes were recorded from stage 2 sleep at BN and 7 during the RN. Movement artefacts prevented the detection of an EEG pattern in 2 of the 9 (22.2%) episodes (2 from RN). The distribution of post-arousal patterns for the stage 2 episodes was: pattern II (22.2%), and pattern III (55.5%). There was no significant difference in the distribution of post-arousal patterns observed during episodes from SWS and stage 2 sleep. Overall, delta activity was detected in 48.6% of sleepwalking episodes from SWS and in 22.2% of those from stage 2. There was no evidence of complete awakening during any of the episodes.

Conclusion: The data indicate that the EEG associated with sleepwalking episodes arising out of stage 2 can be classified according to the same patterns that characterize episodes from SWS. Our results are consistent with those of Schenck et al. who found that nearly half of all post-arousal recordings from SWS contain delta activity and indicate that episodes from stage 2 can also show delta activity. Finally, our findings support the conception of somnambulism as a disorder of arousal and suggest that the sleepwalkers' atypical arousal reactions can manifest themselves similarly in stage 2 sleep as in SWS.

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Comparison of Clinical Characteristics and Polysomnographic Features between Subjects with Idiopathic RBD (REM sleep behavior disorder) and RBD-associated with CNS Disorders

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Introduction: REM sleep behavior disorder (RBD), characterized by excessive motor activity during REM sleep, is associated with loss of muscle atonia. Consequent dream-enacting behavior in RBD patients can be harmful and even injurious to bed partner or patient himself (or herself). In recent years, it has been reported that RBD has high co-morbidity with CNS disorders (especially, Parkinson's disease, dementia, multiple system atrophy, etc.). We aimed at assessing differences of clinical and polysomnographic findings among RBD patients, depending on the presence of CNS disorders.

Methods: Medical records and polysomnographic data of 79 patients who had been diagnosed as RBD at Seoul National University Hospital from June 1992 through October 2003 were reviewed. Diagnosis of

RBD was made on the basis of the presence of RWA(REM without atonia) on the polysomnographic finding, regardless of the presence of associated behavior. The patients were classified into two groups: idiopathic RBD (iRBD, i.e., without clinical history and/or laboratory finding of CNS disorder) group or associated RBD (aRBD, i.e., with clinical history and/or laboratory finding of CNS disorder) group. Fifty-nine patients (74.7%) belonged to iRBD group and 20 patients (25.3%) to aRBD group, being associated with Parkinson's disease (11), multiple system atrophy (2), dementia without parkinsonism (2), olivopontocerebellar atrophy (2), cerebral infaction (1), pontine swelling (1) or brain tumor (1). Clinical characteristics and polysomnographic findings between iRBD and aRBD groups were compared.
Results: Periodic limb movement disorder (PLMD) was more frequently noted in the aRBD group than in the iRBD group (PLMI>5, 85.0% vs. 40.0%, Fisher's exact test, $p<0.05$). Also, obstructive sleep apnea syndrome (OSAS) was more frequently observed in the aRBD group (AHI>5, 80.0% vs. 40.7%, Fisher's exact test, $p<0.05$). Among sleep parameters, slow wave sleep% and sleep efficiency% in the aRBD group were significantly lower than those in the iRBD group (0.3±0.7% vs. 2.7±3.8%, Mann-Whitney U test, $p<0.05$; 64.6±13.1% vs. 77.8±14.5%, Mann-Whitney U test, $p<0.05$, respectively). However, no significant differences of sleep latency, REM sleep%, REM latency, and total sleep time were found. No significant differences between iRBD and aRBD groups were found in age, sex, body mass index (BMI), sleep-related injury, dream-enactment and proportion of subclinical RBD (i.e., RWA only or RWA with minor behavior or sleep talking).
Conclusion: In this study, we found that about 1 out of 4 RBD patients had an association with CNS disorder, warranting more careful neurologic evaluation and follow-up. More than or at least 80% of RBD patients associated with CNS disorder also had PLMD or OSAS and their sleep architecture showed lower slow wave sleep% and sleep efficiency%. These findings suggest that RBD patients associated with CNS disorders are very often be co-morbid with other sleep disorders, demonstrate poorer sleep quality and need more careful clinical attention than the idiopathic RBD patients.

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Nocturnal Groaning: Co-morbility With Other Parasomnias

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Introduction: Nocturnal Groaning (NG) is a sleep-related respiratory phenomenon which is characterized by a deep inspiration, followed by a short expiratory phase and then a long period where the breathing signals are flat or significantly reduced. These hypopneic phases produce a typical monotonous vocal noise. The pitch and timbre of NG appears to vary among patients, but is fairly constant within each subject. The origins of NG remain unexplained. Up to date, only 14 patients are described in the literature (Vetrugno R et al. Neurology 2001; Pevernagie DA et al. Sleep Med 2001) and, for this reason, NG does not fit within the categories of sleep disorders proposed by the American Academy of Sleep Medicine (AASM). Aim of this study was to describe the clinical and polysomnography pictures of consecutive patients with NG, focusing on familial aggregation of the disorders and on the presence of co-morbility with other parasomnias.
Methods: During a two-year period (2001-2002), we observed 15 patients (8 males and 7 female; mean age of 29.8 years (range 18-43)) presenting with clinical data strongly suggestive for NG. Ten patients underwent to a complete video-polysomnography, including EEG, EOG, EMG (mylohyoid, intercostal, anterior tibialis and rectus abdominis muscles), ECG, oronasal flow, thoracic and abdominal efforts, oxygen saturation, sounds.
Results: The mean age of NG onset was 22.5 years; the reported frequency of NG ranged from 1 to several episode per night; none of the patients showed neurological and/or pulmonary diseases. Only one patient reported excessive daytime sleepiness. Five patients reported familial cases of parasomnias (bruxism, sleepwalking; sleeptalking, sleep terrors). In one family, 3 cases of NG, 3 of sleeptalking and 2 of bruxism have been found.Ten patients underwent a full video-polysomnography. Six of these showed a typical NG pattern (hypopneic episodes producing a typical monotonous vocal noise). The NG episodes were both isolated and in short sequences, lasting 7 seconds to 4 minutes, without muscular effort and influence of body position. Sleep structure was normal. There was a great prevalence for REM sleep-related episode (about 70 % of NG episodes occurred in REM sleep). In two patients polysomnography confirmed also the presence of bruxism.
Conclusion: Although NG does not fit within the categories of sleep disorders proposed by the AASM, it seems to be reasonable, on the basis of clinical and polysomnography, to include this among parasomnias of both NREM and REM sleep (i.e. Other Parasomnias). In agreement with Pevernagie DA et al 2002, in about one third of cases we found a familial aggregation with other parasomnias. Moreover, we found a co-morbility with bruxism in two patients. Finally, we reported the first cases of familial NG.

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ICSD-R Criteria For Parasomnias: Interobserver Reliability

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Introduction: Interobserver reliability (IR), that is the degree of agreement among different observers, is necessary to standardise diagnostic procedures, useful when designing multicenter surveys. The diagnosis of most of parasomnias according to the International Classification of Sleep Disorders Revised (ICSD-R) is based on clinical interview. This study determined the IR of these criteria that is still unknown.
Methods: Fifty consecutive patients referred to our sleep centre were included. They underwent a standardized interview by three medical doctors (2 certified neurologists and 1 general practitioner) based on the ICSD-R criteria for the diagnosis of 13 parasomnias: confusional arousals, sleepwalking, sleep terrors, rhythmic movement disorder, sleep starts, sleeptalking, nocturnal leg cramps, nightmares, sleep paralysis, REM sleep behaviour disorders (RBD), sleep bruxism, sleep enuresis, primary snoring. For the first criterion and the final diagnosis of each parasomnia the IR among the three raters was calculated according to the formula by generalization of Kappa for more than two raters.
Results: The 50 subjects were interviewed on average by 2.2 raters (11 by three raters and 39 by two raters). In the group of Arousal Disorders, confusional arousals showed a "substantial" IR (kappa 0.74); sleepwalking showed a "fair" IR (kappa 0.36) despite an "almost perfect" IR of the first criterion (kappa 0.92). Sleep terrors showed a "fair" IR (kappa -0.02), due to a disagreement on all criteria. In the group of Wake-Sleep Transition Disorders, rhythmic movement disorder, sleeptalking and cramps showed "substantial" to "almost perfect" IR, whereas sleep starts showed a "moderate" IR for the first criterion and final diagnosis (both kappa 0.41). In the group of Rem Sleep Parasomnias, sleep paralysis showed a "substantial" IR (kappa 0.69); RBD showed a "moderate" IR (kappa 0.46) and the source of disagreement was the first criterion (kappa 0.39); nightmares showed a "fair" IR (kappa 0.25) due to a disagreement on all criteria. In the group of Other Parasomnias, bruxism, enuresis and snoring showed "substantial" to "almost perfect" IR.
Conclusion: Our study demonstrated that when the clinical diagnosis of parasomnias is based on ICSD-R, 1) the majority of Arousal Disorders and REM sleep Parasomnias showed a "fair" to "moderate" IR; 2) all the

other parasomnias showed a "substantial" to a "almost perfect" IR. The former group with unsatisfactory IR share a complex motor phenomenology associated with a patient's mental state difficult to define. We think that the source of disagreement was the ambiguity of patients' reporting and the difficulty in interpreting their complaints. This hypothesis is reinforced by the excellent agreement of parasomnias where a "simple motor" phenomenology is the main feature. As consequences, 1) for a reliable diagnosis of "simple motor parasomnias" the application of ICSD-R criteria is sufficient; 2) for the diagnosis of parasomnias with complex motor phenomenology or mental state, IR must be verified and eventually improved with training. Moreover, an effort is needed to define better the diagnostic criteria.

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REM Sleep Without Atonia In Progressive Supranuclear Palsy

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Introduction: REM sleep behavior disorder (RBD) is a parasomnia characterized by the occurrence of complex motor activity with a concomitant loss of muscle atonia during REM sleep. It has been hypothesized that RBD and REM sleep without atonia (RSWA) are strongly associated with synucleinopathy disorders (Parkinson's disease, dementia with Lewy bodies and multiple system atrophy) but are rare and only sporadically reported in non-synucleinopathy disorders [Alzheimer's disease, frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy (PSP)]. The aim of the present study was to quantify the time spent with muscle activity during REM sleep in patients with PSP.
Methods: Six patients with PSP (5 men; mean age, 70.5 ± 6.0 years; mean disease duration, 5.9 ± 4.4 years) and 12 healthy controls (10 men; mean age, 69.2 ± 4.7 years) were studied in a sleep laboratory for one night. PSG recordings included EEG, EOG, chin EMG and infrared video monitoring to detect movements during REM sleep. REM sleep was scored using the method of Lapierre and Montplaisir (1992) which allows the scoring of RSWA. The percentage of time spent with muscle activity during REM sleep was quantified by two different methods. The first method (method 1) is that of Lapierre and Montplaisir in which each page of REM sleep is marked either tonic or atonic (tonic = 50% of the page or more is occupied by EMG activity). The second method (method 2) was to cumulate the duration of all periods of EMG activity during REM sleep with an amplitude at least twice that of the background or greater than 10μV and divide by the total REM sleep duration. REM density was scored by calculating the percentage of two-second mini-epochs of REM sleep containing at least one eye movement.
Results: Between group comparison showed a decrease percentage of REM sleep in patients with PSP compared to controls (8.1 ± 4.1% vs 17.1 ± 5.5%: p=0.003). Three of 6 patients with PSP and none of the controls had a major loss of muscle atonia during REM sleep (> 50% of the total REM sleep). In addition, patients with PSP showed a significant increase in the percentage of time spent with muscle activity during REM sleep in comparison to controls and this for method 1 (50.0 ± 45.2% vs 16.0 ± 12.0%: p=0.024) and method 2 (50.9 ± 43.8% vs 16.7 ± 11.4%: p=0.019). Despite the loss of muscle atonia, no behavioral manifestation during REM sleep was observed in PSP patients at the time of the recording but the video tapes were not available for detailed analysis. Patients also showed the expected decrease in REM density compared to controls (10.5 ± 6.8% vs 22.0 ± 11.6%: p=0.04).
Conclusion: These results suggest that RSWA could be found in neurodegenerative disorders other than synucleinopathies. These results also stress the similarity between the two quantitative methods of REM sleep EMG activity. Finally, this study confirms the decrease in percentage of REM sleep and in REM density reported in PSP patients.

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Relation Between Dream Content And Movement Intensity In REM Behavior Disorder

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Introduction: Patients with REM sleep behavior disorder (RBD) report vivid dreams and vigorous body movements that appear to be related to their dream content. There are not many systematic studies, however, of the relation between movement intensity in REM and dream content and its modification with clonacepam.
Methods: Fifteen patients (14 men; mean age 67.7) with idiopathic RBD were studied four nights with a polysomnogram with audiovisual recording: two baseline and two nights 3 months after effective clonacepam treatment. Patients were awakened during stage II and 10 minutes after the beginning of the first and last REM periods. We measured dream recall (%), emotional content of the dream, word count and thematic units in each dream. Thirteen healthy men (mean age 67.5) were studied two nights with the same protocol and compared with the baseline nights of the patients. Videotapes containing the 10 minutes previous to the awakenings were reviewed blindly, without knowing the subject type, sleep stage or treatment. The intensity (mild, moderate, and severe), duration and % of REM time with movements were also measured.
Results: Dream recall in REM sleep in the baseline nights was similar in patients and controls (51.8 % vs. 38.77% respectively; Chi-square 1.77; p: 0.1833), with less dreams with neutral content in patients (16/28) than controls (16/19; Chi-square: 3.82; p: 0.050). Violent/highly anxious dreams were only seen in patients, both at baseline (5 reports) and with clonacepam (3 reports) but in only two cases associated with movements of severe intensity. Words and thematic units per dream were similar in patients and controls. At baseline 13.54% (SD 12.2) of the REM time analyzed in patients contained abnormal movements, with 7 REM episodes with severe movements, 27 moderate and 19 only mild. With clonacepam this changed to 3, 14 and 29 respectively (Chi-square: 7,35; p: 0.025) and movement time decreased to 8.97 % (SD:10.5)(p:0.037). Only three controls had movements in the video (6/23 REM episodes), all of mild intensity and brief duration (except for one subject that was murmuring several seconds). Altogether, patients recalled fewer dreams in REM episodes with mild movements (16/48), than in those with moderate or severe ones (33/51; Chi-square 11.06; p: 0.0008). Five of the 10 patients with severe movements did not recall any dream, two recalled a pleasant dream, one a neutral one and two a violent/highly anxious dream. We could not find a clear relationship between movement pattern and type of dream recall or absence of recall.
Conclusion: As a group, patients with idiopathic RBD recall dreams in REM sleep as often as controls, but they have an increased emotional tone. Dream recall increases with the intensity of the movements, although REM episodes with severe movements are not always linked to dream recall nor to violent/highly anxious dreams. Clonacepam decreases movement time and intensity but does not clearly modify dream emotional tone. We hypotesize that dreaming and body movements in RBD may be not necessarely related.

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Sleep Laboratory Diagnosis Of REM Sleep Behavior Disorder

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Introduction: RBD is a parasomnia characterized by a loss of muscle atonia and/or an increase of phasic electromyographic (EMG) activity during REM sleep. PSG abnormalities required for the diagnosis are qualitative rather than quantitative. The aim of this study was to assess the PSG characteristics of REM sleep in clinically diagnosed idiopathic RBD patients, in order to define specific quantitative PSG criteria for the laboratory diagnosis of RBD.

Methods: Forty consecutive patients (32 M, 8 W; mean age: 66.7±6.4 yrs.) fulfilling the ASDA minimal criteria for RBD diagnosis (mean duration of symptoms: 8.6±8.9 yrs.) with no neurological or other sleep disorders, and 20 age and sex-matched healthy control subjects (16 M, 4 W; mean age: 65.2±6.4 yrs.) were studied. All underwent one-night of PSG recording. Sleep was scored in both groups allowing the presence of muscular tone during REM sleep. Percentages of REM sleep atonia and phasic EMG activity, and density of rapid eye movements (REMs) were quantified, following a method previously described. Density of clonic activity (percent of REM sleep spent with EMG activity lasting <100 msec) and percentage of REM sleep spent with EMG activity (including clonic, phasic and tonic activities) were also quantified. Student T-tests and Mann-Whitney U tests were used when appropriate. Receiver-operating characteristic (ROC) curves were calculated in order to determine the sensitivity and the specificity for each REM sleep variable and to determine cut-off values that best classified patients and controls.

Results: No between-group differences were found on sleep architecture, except for the mean number of REM periods (3.5±1.4 in RBD vs. 4.3±1.1 in controls; p=0.01). As expected, RBD patients showed a lower percentage of REM sleep atonia (41.3±30.6 vs 87.8±10.4; p<0.001) and higher percentages of both REM sleep phasic activity (26.3±10.9 vs. 7.9±4.0; p<0.001) and total muscle activity during REM sleep (54.3±30.6 vs. 13.1±10.4; p>0.001) compared to controls. No between-group difference was observed for the density of clonic activity (0.031± 0.024 vs. 0.036± 0.025; p=0.54). REMs density was lower in RBD patients than in controls (17.1±9.0 vs. 21.3±10.4; p=0.02). Among patients with RBD, women had a higher % phasic EMG activity than men (34.4±11.1 vs. 23.9±10.0; p=0.036). Percentage of phasic EMG activity best discriminated the two groups, yielding a sensitivity and a specificity of 90% (cut-off value:13%; area under the curve:87%). Percentage of REM sleep atonia correctly classified 87.5% of patients and 80% of the controls (cut-off value:78.5 %; area under the curve: 84.75%), while total muscle activity showed a sensitivity of 80.5% and a specificity of 80% (cut-off value: 23%; area under the curve:77.6%).

Conclusion: This study showed that % of phasic EMG activity is a more sensitive parameter for diagnosing RBD than % of atonia and therefore it may represent a valuable tool in the laboratory diagnosis of this condition. Results also point to a gender effect on phasic EMG activity. The reduced REMs density in RBD, in spite of the increased phasic EMG activity, suggests an impairment of neural mechanisms implicated in REMs generation.

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Periodic Leg Movements In Rem Sleep Behavior Disorder: Comparison With Age-Matched Healthy Controls

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Introduction: REM sleep behavior disorder (RBD) is a parasomnia characterized by complex motor activity occurring during REM sleep, associated with dream mentation. We previously showed that periodic leg movements (PLM) are very frequent in RBD patients during both non-REM and REM sleep and that EEG activation associated to PLMS was reduced in RBD, compared to patients with restless legs syndrome (RLS). The aim of the present study was to evaluate the frequency, the polysomnographic (PSG) characteristics and the associated EEG activation of PLM in RBD patients compared to age and sex-matched healthy controls.

Methods: Forty consecutive patients (32 M,8 W; mean age: 66.7±6.4 yrs.) diagnosed with idiopathic RBD (mean duration of symptoms: 8.6±8.9 yrs.) with no neurological or other sleep disorders and no symptoms of RLS, and 20 age and sex-matched healthy control subjects (16 M,4 W; mean age: 65.2±6.4 yrs.) were studied. All underwent one- night of PSG recording. Sleep was scored in both groups allowing the presence of muscular tone during REM sleep. PLMS and microarousals (MA) were scored using the standard criteria. PLM indexes during both wakefulness and sleep and MA index were determined for all subjects. PLMS indexes during both non-REM and REM sleep, as well as the % of PLMS associated with MA (%PLMS-MA), were calculated in all those subjects with a PLMS index > 5. Student T-tests and chi-square tests were performed to assess between-group differences on PSG variables. Mann-Whitney U tests were performed when appropriate.

Results: No between-group differences were found on sleep architecture variables. RBD patients showed a higher mean PLMS index compared to controls (26.9±30.9 vs. 13.1±23.3; p=0.008). Moreover, the proportions of subjects with PLMS index >5, >10 or >20 were significantly higher in RBD group than in controls (PLMS ix>5: 30/40(75%) vs. 9/20(45%), p=0.022; PLMS ix>10: 27/40(67.5%) vs. 5/20(25%), p=0.019; PLMS>20: 20/40(50%) vs. 4/20(20%), p=0.025, respectively). No between-group difference was found on PLM index during non-REM sleep (33.7±31.5 vs. 33.3±34.9; p=0.57), but RBD patients showed a considerably higher PLM index during REM sleep compared to controls (44.1±45.9 vs. 3.4±3.3; p<0.0001). No difference was observed in the PLM index during wakefulness, although a trend for a higher PLMW index was observed in RBD (35.5±33.8 vs. 23.3±28.0; p=0.10). The two groups did not differ on MA index (12.0±8.3 vs. 12.4±6.4, p=0.69) nor on % PLMS-MA. However, a trend for a lower %PLMS-MA was observed in RBD patents (7.4±6.4 vs. 19.9±17.4; p<0.072).

Conclusion: This study confirms the higher frequency of PLMS in idiopathic RBD patients compared to age-matched healthy subjects. In RBD patients, PLMS occurred especially during REM sleep, as a possible result of the known lack of motor inhibition. Although elevated, the PLMW index was not significantly different in the two groups. PLMW results in healthy control subjects seems to differ from previously observations, and may be due to the older age of the population. Although the MA index was similar in the two groups, PLMS tended to be less associated with MA in RBD patients, in agreement with previous observations.

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The Correlation Of Obstructive Sleep Apnea Syndrome Severity With Prevalence Of Sleepwalking And Sleep Terrors In Sleep Laboratory Population With Suspected Sleep-Related Breathing Disturbance

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Introduction: Sleepwalking (SW) and sleep terrors (ST) are disorders of arousal from non-REM sleep, typically slow-wave sleep (SWS). Internal or external arousals may trigger episodes of SW or ST in predisposed individuals. We investigated whether more severe obstructive sleep apnea syndrome (OSAS), presumably producing more frequent arousals, correlates with higher prevalence of SW or ST.
Methods: A parasomnia questionnaire and polysomnographic data from 284 patients referred to the Sleep Disorders Center of The Cleveland Clinic Foundation for suspected OSAS were prospectively collected over a 25-week period in 2002-2003. 65 patients with other sleep disorders (periodic limb movement disorder, nocturnal seizures) were excluded. Prevalence of SW and ST was analyzed in the remaining 219 patients divided into four groups (no OSAS, mild, moderate, and severe OSAS).
Results: Age ranged from 2 to 80 years. 63.5% were males. Mean age was 35.8, 47.7, 49.4, and 50 years in the four studied groups, respectively. Arousal index (AI) was 12.4, 18, 25.7, and 47.3, respectively. SWS accounted for 15, 8.1, 8.5, and 5% of total sleep time in the four groups, respectively. Both the lifetime and last-year prevalence of SW/ST was significantly lower in the OSAS subjects. The lifetime prevalence was 28.9, 13.6, 11.9, and 9.1%, respectively. The last-year prevalence was 17.8, 6.1, 4.8, and 3%, respectively.
Conclusion: Increased AI associated with more severe OSAS did not result in increased prevalence of SW/ST. Both the lifetime and last-year prevalence of SW/ST was significantly lower in the OSAS subjects. Such factors as the lower amount of SWS and higher age in the OSAS subjects may have contributed to this finding.

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Diagnostic Value of Video Electroencephalography Polysomnography in Patients with Unusual Behaviors at Night

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Introduction: It has been reported that 20% of epilepsy patients only have their seizures during sleep. Despite this high frequency of nocturnal seizures, it is often difficult to determine clinically whether unusual behavior during sleep represents epilepsy or parasomnia. Often long-term video monitoring is performed in an epilepsy monitoring unit which is costly and labor intensive. An alternative is to combine video electroencephalography (VEEG) and polysomnography (PSG) which is typically done during one night in a sleep laboratory. There has been one study that found that the VEEG-PSG is a helpful tool for diagnosing parasomnias and seizures.
Methods: A retrospective analysis was done on 50 VEEG-PSGs conducted in patients without a known history of epilepsy to evaluate unusual nocturnal behaviors. The studies were performed at the Cleveland Clinic Foundation between January 2000 and December 2003. A definitive diagnosis of parasomnia or epilepsy was made if a typical spell was recorded on video or if epileptiform activity was recorded. A probable diagnosis was made if there were supportive findings such as arousals out of slow wave sleep (SWS). A study was considered non-diagnostic if there was no recorded episode or no supportive findings
Results: Of the 50 identified VEEG-PSGs (32 males, 18 females), a definitive diagnosis was made in 9 (18%) patients. 5 (10%) had a typical spell recorded on video and 4 (8%) had EEG epileptiform abnormalities. A probable diagnosis was made in 10 (20%) patients. Of the 15 patients with SWS arousals, 10 (20%) had no associated clinical activity, whereas 5 (10%) had associated clinical activity. 31 (62%) had no findings on PSG or EEG to support a diagnosis of parasomnia or epilepsy. However, among the non-diagnostic studies, sleep disordered breathing was found in 23 (74%). There were 19 pediatric patients (mean age 8, 16 males, 3 females). In the pediatric group, 4 (21%) had a definitive diagnosis (2 with typical spells recorded on video, 2 with EEG epileptiform abnormalities), and 11 (58%) had a probable diagnosis (arousals out of SWS with no associated clinical activity). There were 31 adult patients (mean age 41, 16 males, 15 females). In the adult group, 5 (16%) had a definitive diagnosis (3 with typical spells recorded on video, 2 with EEG epileptiform abnormalities), and 2 (7%) had a probable diagnosis (arousals out of SWS with no associated clinical activity).
Conclusion: This is a preliminary study looking at the usefulness of VEEG-PSG in making a definitive or probable diagnosis of parasomnia or epilepsy when evaluating unusual behaviors during sleep. VEEG-PSG seems to be a helpful tool when investigating unusual behaviors during sleep in patients without a known history of epilepsy. Further work is being done to delineate this possibility.

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An Open Label Study Of oxcarbazepine in Restless Legs Syndrome (RLS)

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Introduction: There have been no previous trials of oxcarbazepine in Restless Legs Syndrome (RLS). Carbamazepine (Tegretol) was found to be effective for RLS but has many serious side effects such as neutropenia and liver dysfunction, oxcabazepine has a similar chemical structure but without the neutropenia and the liver dysfunction, so we tried to determine if it is effective in the treatment of Restless Legs Syndrome.
Methods: 17 RLS patients (10 females and 7 males, age range 28-82 years and average 46 years) were given oxcarbazepine(range 600-1500 mg and average 900 mg) as an open label monotherapy or an add on drug for RLS. Dosages of the other RLS medications were kept stable throughout the study. The international Restless Legs Syndrome Study Group Rating Scale (IRLS) was adminestred before and after therapy.
Results: 4 patients dropped from the study because 2 did not feel any relief of the symptoms and 2 developed side effects such as dizziness, confusion and nausea. No rating scale values after therapy were obtained on these four patients. With intension to treat/ last Observation Carried Forward analysis, the average IRLS prior to therapy was 28.9 (range 25-39), whereas the average IRLS after therapy was 9.1 with a p value of <0.001
Conclusion: Oxcarbazepine (Trileptal) appears to be an effective therapy and well tolerated for the treatment of RLS as a monotherapy or an add on medication. Even with ITT/LOCF analysis, there is a 20 points difference between the drug and placebo on the IRLS, which is much greater than the 8 points placebo effect seen in previous large scale therapy studies of other agents in the treatment of RLS. This observation will have to be documented in blinded studies which include IRLS as well as polysomnography and actigraphy.

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Apomorphine In Idiopathic RLS: An Exploratory Study

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Introduction: Both, opioidergic and dopaminergic drugs have been found to be effective in RLS patients. In case studies, naloxone, an opioid antagonist (acting at mu, kappa, and sigma opioid receptors), could antagonize the treatment effects of propoxyphene and methadone; pimozide, a D2 receptor antagonist, could partially antagonize the treatment effects of codeine sulfate. There are only a few, poorly documented case reports on apomorphine (10,11 dihydroxyaporphine), a combined opioidergic and dopaminergic agonist, in RLS. This study was performed to document apomorphine effects in idiopathic RLS (iRLS). We tested the effects of apomorphine and subsequent selective antagonisation by naloxone and metoclopramide on subjective and objective symptoms in patients with iRLS.
Methods: Nine patients (mean age 55 yrs) with a severe iRLS were examined. In a one-night polysomnography, PLMS index was greater 10 per hour of total sleep time, apnea index was lower 5 per hour total sleep time. The patients were pretreated with oral domperidone for three days. A modified Suggested Immobilization Test (SIT) was performed between 8 p.m. to 1 a.m. under the following conditions of intravenous drug administration: baseline; apomorphine; apomorphine and naloxone; apomorphine and metoclopramide. Outcome parameters were a visual analogue scale (VAS) of subjective RLS symptoms and EMG documented periodic leg movements while awake (PLMW).
Results: As compared to baseline, apomorphine showed a rapid and significant improvement of subjective RLS symptoms, measured by VAS (54.5% improvement; $p = 0.011$), and an almost immediate cessation of PLMW, measured by PLMW index (98.0% improvement; $p = 0.012$). These effects were reached in most patients with the initial bolus of 0.035 mg/kg body weight and with a constant infusion rate of up to 0.04 mg/kg/h. Neither additive naloxone nor metoclopramide could block this effect significantly. On apomorphine with metoclopramide, patients showed a trend towards reappearance of PLMW. After the initial bolus of apomorphine side effects like drowsiness, dizziness, and nausea occurred.
Conclusion: Apomorphine may be an effective treatment in iRLS. Its effectiveness might be due both to its dopaminergic and opioidergic activity, which could not be antagonized significantly by blocking of only one of these pathways. The trend towards worsening of the PLMW index following metoclopramide administration might be a hint for a primarily dopaminergic effect of apomorphine in iRLS.

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Apoptosis Is The Cause Of Substantia Nigra Dopaminergic Cell Death Induced By Iron Deprivation And Opioid Prevent This: A Possible In Vitro Model For Restless Legs Syndrome

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Introduction: Hypofunction of the endogenous dopaminergic and opioid systems in the brain have been implicated in the pathogenesis of Restless legs syndrome (RLS) as has iron deficiency. The major cells in the substantia nigra (SN) are dopaminergic and cell cultures of these cells were chosen to create an iron deficiency model of RLS. Previously we reported that iron deficiency causes damage and cell death of the SN cells and that the d-opioid by [D-Ala2, D-Leu5]Enkephalin (DADLE) protects against SN cell damage caused by iron deprivation. In this study we investigated whether the damage caused by iron deprivation is due to iron nutritional deficiency or due to iron deprivation induced neuronal apoptosis.
Methods: Cell cultures of SN cells from Sprague-Dawley rats were established. Three groups of experiments were done: a). Cells were exposed for 48 hours to 0 μM, 1 μM, 10 μM and 100 μM of desferoxamine (DFO) which binds to iron and causes iron deficiency of the cells; b). Cells were exposed first to 100 μM of the delta opioid peptide DADLE followed 2 days later by 48 hour exposure to 50 and 100 μM of DFO; c). Cells were exposed to 100 μM of DFO for different durations: 6, 12, 24 and 48 hours. Each group had a control exposed to neither DFO nor DADLE. The quantity of cells was recorded up to 3 weeks after the different treatments. Student t-test and ANOVA with a $p < 0.05$ were used to determine statistical significance.
Results: The numbers of SN cells under culture were significantly reduced 7 days after 48-hour exposure to either 10 μM or 100 μM DFO ($p < 0.01$ for both concentrations compared to control). With 100 μM DFO, cells exposed for over 24 hours exhibited significant delayed cell death indicative of apoptosis, while no significant damage were observed for exposure for only 6 hours and 12 hours. We also did experiments to determine if DADLE is able to rescue some cell death caused by short DFO exposure. DADLE alone (100 μM) did not cause significant cell growth compared to the control ($p > 0.05$). However, DADLE at 100 μM significantly protected against cell death by 48 hour exposure to 100 μM DFO compared 100 μM DFO alone ($p < 0.05$).
Conclusion: This study provides evidence that iron deficiency causes damage and cell death of the SN cells through cell apoptosis, and that DADLE protects SN cell from apoptosis induced by iron deficiency. Our previous histochemical work has shown that these cells are dopaminer-

gic. The evidence of studies to date suggests that iron deficiency causes dopaminergic dysfunction can be prevented by opiate treatment. This evidence also suggests that an intact endogenous opiate system is necessary to prevent the symptoms of RLS. In our iron deprivation RLS model, more experiments are under way to detect the fragmentation of cellular DNA characteristic of apoptosis and to explore the possibility that opioids prevent such an event. The extension of this model to in vivo is necessary to determine if these animals present with the increased motor activity characteristic of RLS or whether our model would also have pathogenic implications for other dopamine mediated disorders such as the REM sleep behavior disorder and Parkinsons Disease.

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The Impact of Ropinirole Treatment on RLS Symptoms and Health-Related Quality of Life (HRQoL) in Patients with RLS: Results of a Multinational 36-Week Study

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Introduction: RLS (Ekbom syndrome), a neurological movement disorder, produces sensory disturbances and leg movements that have profound effects on sufferers' ability to sleep. Sufferers also show markedly impaired HRQoL compared with the general population. Alleviation of sensorimotor symptoms is expected to result in improved sleep and HRQoL. One of the objectives of this 36-week international study was to assess the changes in these two parameters following ropinirole treatment (protocol: 101468/188).
Methods: Patients (18-79 years) with primary RLS received 24 weeks' single-blind (SB) ropinirole treatment. Ropinirole was titrated to its optimal therapeutic dose (range: 0.25-4.0 mg/day); no further titration was allowed after week 20. At the end of the SB phase, patients meeting the criteria for treatment continuation were randomized to 12 weeks of double-blind (DB) treatment with ropinirole or placebo. The primary endpoint was the proportion of patients relapsing during the DB phase. Relapse was defined as either i) an International Restless Legs Scale score of 15 or more (moderate-to-severe RLS) that had worsened by at least 6 points compared with the start of DB treatment, or ii) withdrawal due to lack of efficacy. Changes in HRQoL during the DB phase were measured using a disease-specific scale (RLS Quality of Life questionnaire, RLSQoL) and a generic instrument (Short Form (SF)-36). Sleep parameters were measured using the Medical Outcomes Study (MOS) sleep scale.
Results: 106/202 patients completed the SB phase; 92 were randomized to DB treatment. The odds of a patient relapsing while receiving placebo were three times greater than those of a patient receiving ropinirole (32.6% vs 57.8% relapsed with ropinirole and placebo, respectively; adjusted odds ratio: 0.33; 95% CI: 0.13, 0.81; p=0.0156). In the DB phase, the change in the RLSQoL overall life impact score showed a significant treatment difference in favor of ropinirole (adjusted mean treatment difference: 11.8 points; 95% CI: 3.9, 19.7; p=0.0040). Treatment differences favored ropinirole in all domains of the SF-36, reaching significance in four: role limitations due to physical health problems, vitality, social functioning and mental health. During the SB phase, patients showed improvements on all four domains of the MOS sleep scale (sleep disturbance: -26.7 points; daytime somnolence: -12.7 points; sleep quantity: 48 minutes; sleep adequacy: 20.5 points). Compared with patients continuing to receive ropinirole, patients switching to placebo during the DB phase experienced significant worsening in sleep disturbance (adjusted treatment difference: -21.0 points; 95% CI -31.9, -10.1; p=0.0003), daytime somnolence (-9.1 points; 95% CI -16.4, -1.9; p=0.0136) and sleep quantity (60 minutes; 95% CI 6, 120; p=0.0346). Treatment differences in favor of ropinirole were also observed for sleep adequacy, although these were not statistically significant (adjusted mean treatment difference = 9.1; 95% CI: -2.1, 20.2; p=0.1102). The most common adverse events were nausea and headache. Most adverse events were mild or moderate in severity.
Conclusion: Ropinirole was effective in the long-term management of RLS symptoms and its attendant secondary problems, such as sleep disturbance and impaired HRQoL. Ropinirole was well tolerated.

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Pramipexole Is Safe And Efficacious In The Treatment Of Idiopathic Restless Legs Syndrome: Results Of A Large Randomized Double-Blind Placebo-Controlled Dose-Finding Study

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Introduction: According to isolated reports, restless legs syndrome (RLS) associated with periodic limb movements during sleep (PLMS) has successfully been treated with low-dose pramipexole. However, no data on the optimal dose are currently available. Therefore we performed a dose-finding study to determine the optimal dose of pramipexole in the treatment of patients with idiopathic RLS and PLMS.
Methods: This was a three-week double-blind placebo-controlled dose-finding study. Patients received once daily either placebo or 0.125 mg, 0.25 mg, 0.5 mg, or 0.75 mg pramipexole (fixed dose). All patients in the pramipexole groups were started on 0.125 mg/day. For the higher dose groups, the dose was increased stepwise. The final dose was reached on day 5 (0.25 mg), day 9 (0.5 mg), and day 13 (0.75 mg). Patients were assessed by polysomnography at baseline and at week 3. The primary endpoint was the reduction in periodic limb movements during time in bed (PLMI). Secondary endpoints were the reduction in periodic limb movements during sleep (PLMSI) and during wakefulness (PLMWI). In addition, patients assessed the severity of RLS symptoms using the RLS Rating Scale for Severity (RLSRS) at baseline and at week 3. These endpoints were analysed by ANCOVA on log-transformed data to account for non-normal distribution. Safety was assessed by physical examination, ECG, clinical laboratory tests, and occurrence of adverse events.
Results: In total 109 patients were randomized to either placebo (n=22), or pramipexole at a daily dose of 0.125 mg (n=21), 0.25 mg (n=22), 0.5 mg (n=22), or 0.75 mg (n=22). One patient in the placebo group and 1 patient in the 0.125 mg group discontinued the study prematurely; 98.2% of patients completed the study. The mean age was 56.2 years, 73.8% of patients were female, 41.1% of patients had received previous treatment for RLS, 58.9% were de-novo patients. The adjusted mean PLMI at baseline was 42.1 (placebo), 42.1 (0.125 mg), 32.8 (0.25 mg), 34.5 (0.5 mg), and 34.1 (0.75 mg). At the end of week 3, the adjusted means were 35.5 (placebo), 6.9 (0.125 mg), 5.0 (0.25 mg), 4.9 (0.5 mg), and 7.6 (0.75 mg); p<0.0001 vs. placebo for all dose groups. PLMSI and PLMWI exhibited similar patterns. The adjusted mean RLSRS scores at baseline were similar in all treatment groups with 22.9 (placebo), 22.4 (0.125 mg), 23.0 (0.25 mg), 23.6 (0.5 mg), and 21.7 (0.75 mg). The adjusted mean reductions in RLSRS were -6.3 (placebo), -12.4 (0.125 mg), -14.4 (0.25 mg), -17.0 (0.5 mg), and -15.9 (0.75 mg), p<0.0054 vs.

placebo for all dose groups. At the end of week 3, the percentages of patients who had experienced a drop of at least 50% in their RLS rating were 33.3% (placebo), 61.9% (0.125 mg), 68.2% (0.25 mg), 77.3% (0.5 mg), and 76.2% (0.75 mg). The overall incidences of adverse events were similar in all groups. Nausea was reported for 4.5% of patients in the placebo group (maximum intensity: moderate), and for 14.9% of patients in the pramipexole groups (maximum intensity: mild). Headache was more frequent in the placebo group (36.4%) than in the pramipexole groups (4.8%, 18.2%, 31.8%, and 22.7%). The incidence of fatigue was similar in all groups (22.7%, 23.8%, 13.6%, 27.3%, and 9.1%, respectively). No patient in the placebo group and in the 0.5 mg group but 1 patient in each of the remaining dose groups reported somnolence; insomnia was only reported in the placebo group (9.1%). Orthostatic hypotension was noted for one patient (0.125 mg).
Conclusion: Polysomnographic assessment showed efficacy of pramipexole in the treatment of RLS over the dose range of 0.125 mg/day to 0.75 mg/day within 3 weeks of therapy. Clinical efficacy based on RLSRS score and responder rate (≥ 50% reduction in RLSRS) was most prominent in the 0.5 mg and the 0.75 mg groups. Safety and tolerability were favourable in all dose groups tested. The overall study results support the concept of an individually optimized therapy for RLS based on pramipexole in the range of 0.125 mg/day to 0.75 mg/day.

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Maintained Efficacy with Ropinirole: Results of a Multinational 36-Week Study of Patients with RLS

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Introduction: RLS (Ekbom syndrome) is a neurological movement disorder characterized by sensory disturbances and repetitive stereotypic leg movements. These symptoms have a major impact on the sufferer's ability to initiate and maintain sleep. Three large, double-blind, placebo-controlled studies have shown that ropinirole alleviates RLS symptoms and improves sleep over 12 weeks of treatment. However, RLS is a chronic disorder and longer-term studies are also required. This study was designed to evaluate the long-term efficacy of ropinirole treatment in RLS (protocol: 101468/188).
Methods: Patients aged 18-79 years who had primary RLS received single-blind (SB) ropinirole treatment for 24 weeks. During this time, ropinirole was titrated to an optimal therapeutic dose (range: 0.25-4.0 mg/day); no further titration was allowed after week 20. At the end of the SB phase, patients who met the criteria for treatment continuation were randomized to double-blind (DB) treatment with ropinirole or placebo for 12 weeks. Patients randomized to placebo underwent a 2-week blinded down-titration of ropinirole; those randomized to ropinirole continued treatment with the dose reached during the SB phase. The primary endpoint was the proportion of patients relapsing during the DB phase. A relapse was defined as either i) an International Restless Legs Scale (IRLS) score of 15 or more (moderate-to-severe RLS) that had increased (worsened) by at least 6 points compared with the start of DB treatment, or ii) withdrawal due to a lack of efficacy. Secondary endpoints included the proportion of patients with a score of much or very much improved on the Clinical Global Impression-Improvement (CGI-I) scale at week 36, and the change in IRLS score between weeks 24 and 36.
Results: 106/202 patients completed the SB phase with 92 randomized to DB treatment. At week 20, after which dose changes were not allowed, the median ropinirole dose was 2.0 mg/day. The odds of a patient relapsing while receiving placebo were three times greater than those of a patient receiving ropinirole (32.6% vs 57.8% relapsed with ropinirole and placebo, respectively; adjusted odds ratio = 0.33; 95% CI: 0.13, 0.81; p = 0.0156). Similarly, the secondary endpoints showed significant treatment differences in favor of ropinirole. The proportion of patients with a score of much or very much improved on the CGI-I scale was greater for ropinirole (adjusted odds ratio = 2.6; 95% CI: 1.1, 6.3; p = 0.0298) and the change in IRLS score was smaller for ropinirole than placebo (adjusted mean treatment difference = -4.6 points; 95% CI -8.6, -0.6; p = 0.0246). The most common adverse events were nausea and headache. During the trial, three patients (1.5%) experienced augmentation (reported as hyperkinesia) during ropinirole treatment; this worsening of symptoms resolved spontaneously after a period of continued treatment with ropinirole.
Conclusion: Ropinirole was effective and well tolerated in the long-term management of RLS.

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An Early Onset of Action in RLS: Results from the Ropinirole Clinical Trials Program

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Introduction: Symptoms of the chronic neurological movement disorder, RLS (Ekbom syndrome), can seriously impact on patient sleep and quality of life (QoL). Data from the ropinirole clinical trials program have shown that this agent alleviates symptoms and improves sleep and QoL over 12 and 36 weeks. In terms of the rapidity of onset to clinical improvement, small, short-term studies have suggested the benefits of ropinirole treatment are apparent within 1 day. Data from large, double-blind clinical trials are needed to confirm a rapid onset of effect. The present analysis investigates the efficacy of ropinirole after 1 week of therapy using data from three such trials (protocols: 101468/190, 101468/191 and 101468/194).
Methods: Combined data from three double-blind, placebo-controlled trials with common methodology were included in the analysis. Patients (18-79 years) with primary RLS were randomized to ropinirole or placebo (1:1) for 12 weeks. Patients receiving medication for RLS or sleep disorders before the study entered a washout period. During weeks 1-7, ropinirole was titrated upwards (range: 0.25-4.0 mg/day) to reach patients' individual efficacious doses. The maximum dose by the week-1 visit was 0.5 mg/day. Treatment was administered once daily, 1-3 hours before bedtime. The proportion of patients assessed as much improved or very much improved on the Clinical Global Impression Improvement (CGI-I) scale at week 1 and the change from baseline to week 1 in the International Restless Legs Scale (IRLS) total score were prospectively defined key secondary endpoints for two and three of the studies, respectively.
Results: A total of 618 patients were randomized (mean ropinirole dose during week 1 was 0.45 mg/day). The mean ages in the ropinirole and placebo groups were 54.5 and 55.8 years, respectively, and there were

more women than men (59.5% and 62.7%, respectively). Participants had been suffering from RLS for just under 20 years (ropinirole, 18.0 years; placebo, 19.3 years). Significantly more patients in the ropinirole group (35.3%, 109/309) reported their condition as much improved or very much improved on the CGI-I scale at week 1 (last observation carried forward) compared with the placebo group (14.8%, 45/304; adjusted odds ratio: 3.1; 95% CI: 2.1, 4.7; $p < 0.0001$). Similarly, the mean improvement in the IRLS score at week 1 (observed case) was significantly greater for ropinirole (-8.1 [SE = 0.46], n = 299) compared with placebo (-4.6 [0.46], n = 290; adjusted mean treatment difference: -3.5 points; 95% CI: -4.6, -2.4; $p < 0.0001$).
Conclusion: The onset of action of ropinirole treatment was rapid, even at the low doses (0.25-0.5 mg/day) utilized in the first week of the studies. Studies have shown that significant improvements in RLS symptoms are also seen at week 12 using mean ropinirole doses of approximately 2 mg/day. In clinical practice, optimal dosing must be individualized.

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Actigraphy for PLM Detection: A Validation Study with Polysomnography

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Introduction: Actigraphy is a simple tool to quantify motor activity during sleep. Actometers with specific software to detect periodic limb movements (PLM) are increasingly used to assess treatment effects on PLM in patients with Restless Legs Syndrome (RLS). Several actometers with PLM software are available, but adequate validation studies against the gold standard polysomnography are lacking for PLM measurements.
Methods: 24 patients (mean age 57.5 +/- 12.0 years) with a PLM index (PLMI) > 5 per hour in a previous polysomnography (PSG) participated in the study; 12 had RLS/PLMS, 12 had PLMS without RLS. All patients underwent a full night (8 hours) of digital PSG (Schwarzer Brainlab, Munich, Germany) and simultaneous actigraphy from both legs (Actiwatch with PLMS Software V.2.36, Cambridge Neurotechnology UK). For analysis, PSG and actigraphy were displayed in simultaneous 1 minute windows. In PSG, PLM were manually counted according to standard criteria (Sleep 1993;16: 748-759). Actigraphic PLMIs were obtained automatically for TIB and manually for NonREM, REM and wakefulness. The min/max ratio, a measure of spread in periodicity of PLM, was set at 0.5 (default). A subanalysis was done for PLM counts from one leg against PSG from both legs.
Results: The polysomnograpic PLMI was 34.4 +/- 30.7 PLM/hour (h) time in bed, the actigraphic PLMI was 21.2 +/- 25.6 PLM/h TIB ($p<0.001$, Wilcoxon test). Only 61.6% of the PLM in PSG were detected by the actiwatch. However, there was a high correlation of PSG and actigraphy derived PLMI (Spearman's correlation coefficient $r=0.835$, $p<0.001$). The state specific PLMIs in PSG and actigraphy were: NonREM sleep: 27.5 +/- 24.3 versus 16.7 +/- 21.8 ($p<0.001$;$r=0.863$,$p<0.001$); REM: 1.51 +/- 2.7 versus 0.8 +/- 1.4 ($p = 0.07$, $r = 0.661$, $p<0.001$); wakefulness: 5.4 +/- 9.4 versus 3.6 +/- 5.3/h ($p=0.18$, r=0,837,$p<0.001$). Unilateral actigraphy gave a total PLMI of 16.9 +/- 20.7 for the right, and 6.8 +/- 14.6 for the left leg. The correlation between PLMI from standard PSG and unilateral actometry was $r=0.829$ (right) and $r = 0.553$ (left) ($p<0.001$).
Conclusion: The actiwatch significantly underestimated PLM in comparison with PSG. This may relate to the fact, that EMG activation of the tibial anterior muscle is used to identify PLM in PSG, and manifest movement of the limb in actigraphy. The high correlation between PSG and actigraphic PLMs indicates nevertheless, that actigraphy is useful to identify PLM. PSG and actigraphy cannot be interchanged when doing follow-up studies. Unilateral actigraphy may result in low correlations with PSG and should be considered insufficient for PLM counting.

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Alleviation of Motor Symptoms and Consequent Sleep Benefits with Ropinirole in RLS

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Introduction: RLS is a significant cause of insomnia, and the effect on the quality of life of sufferers can be profound. Data from one study in the ropinirole RLS clinical trial program have shown that, compared with patients receiving placebo, those receiving ropinirole experience significantly greater reductions in the motor symptoms causing sleep arousal (periodic leg movements causing arousal, PLMA). Alleviation of these symptoms is expected to result in improved sleep and is likely to improve QoL. The present analysis investigates the effect of ropinirole on key aspects of sleep using data from three double-blind, placebo-controlled studies from the RLS clinical trial program (protocols: 101468/190, 101468/191 and 101468/194).
Methods: Data from three studies, all with common methodology, were combined. Patients with primary RLS, aged at least 18 years and with an International Restless Legs Scale score of 15 or more, were randomized to ropinirole or placebo (1:1) for 12 weeks. Patients receiving medication for RLS or sleep disorders before the study undertook a washout period. Study medication was titrated to an individual efficacious dose during weeks 1-7 (range: 0.25-4.0 mg/day). Dosages remained stable after week 7 or after reaching the efficacious dose. Treatment was administered once daily, 1-3 hours before bedtime. Patients completed the Medical Outcomes Study (MOS) sleep scale at baseline and week 12; data from four domains were analyzed (sleep adequacy, quantity, disturbance and daytime somnolence).
Results: A total of 618 patients were randomized to treatment (ropinirole, n = 310; placebo, n = 308). The mean ropinirole dose at week 12 (LOCF) was 1.88 mg/day. Improvements from baseline to week 12 were significantly greater for the ropinirole group compared with the placebo group for all four MOS sleep scale domains: sleep adequacy, adjusted mean treatment difference 12.1; 95% CI 7.8, 16.3; $p < 0.0001$; sleep quantity, adjusted mean treatment difference 42 minutes; 95% CI 18, 72; $p = 0.0021$; sleep disturbance, adjusted mean treatment difference -9.6; 95% CI -13.3, -5.9; $p < 0.0001$; daytime somnolence, adjusted mean treatment difference -5.0; 95% CI -7.9, -2.2; $p = 0.0006$. The most common adverse events were nausea and headache; nausea was more common in the ropinirole group than the placebo group. However, few patients withdrew because of nausea (ropinirole, 2.3% [7/309]; placebo, 0.3% [1/307]).
Conclusion: A previous smaller, placebo-controlled polysomnographic study has shown that ropinirole treatment, with the same doses used in this analysis, reduced the motor expression of RLS during the sleep period. This larger study demonstrates that RLS patients treated with ropinirole report subjective improvements in sleep quality and quantity, as expected from the reported benefits on motor symptoms of RLS.

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Repeated IV Doses Of Iron Glucose (Ferrlecit) Provide Effecitve Supplemental IV Iron Treatment Of Restless Legs Syndrome

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Introduction: We showed that a single 1000 mg IV iron treatment provides for 6 out of 10 RLS patients without anemia complete remission of all RLS symptoms for 2 months to 2 years following . BUt serum ferritin decreased 4 to 20x greater than expected for normal. The faster ferritin decreases correlated with fewer weeks before return of RLS symptoms. A rapid loss of the iron stores appears to be occuring in RLS patient. Treatment benefit might be maintained by supplementing the initial treatment with repeated IV iron treatments when RLS symptoms start to return.
Methods: Five RLS patients who responded to an initial 1000 mg IV iron treatment were given open-label supplemental IV iron treatment whenever the returning RLS symptoms warranted medication treatment and also serum ferritin less than 400 mcg/L. Each supplemental treatment was iron-glucose given 150 mg in 5-minute slow IV push repeated 3 times every other day for a total dose of 450 mg. Response was evaluated by RLS-sleep log, global rating, leg activity monitoring, serum ferritin and %SAT measures. Measures were obtained before each IV iron treatment, and at 2 weeks, 4 weeks, and then every 4 weeks after treatment until return of symptoms. Repeat IV iron supplemental treatments occurred for up to 2 years with no more than 4 allowed in 1 year
Results: All 5 subjects showed a positive response to each repeated IV iron treatment; 4 responded for the full 2 years of the treatment program, 1 discontinued at 1 year owing to problems with RLS symptoms returning too rapidly to be managed by the maximum treatments allowed in one year. The subjective responses were matched by significant (>50%) decreases in objective measures of periodic leg movements during sleep. With repeated iron dosing the excessively rapid decline in serum ferritin after IV iron as noted above decreased and the duration of benefit also increased for all patients except for the one with the most rapid decrease who also showed the most rapid return of symptoms. The rate of decline in serum ferritin correlated inversely with duration of symptom relief ($r = 0.71$, $p = 0.003$). The serum ferritin decrease was approximately normal after the last treatment for 2 patients, who both showed treatment benefits lasting at least 2 years. No significant adverse effects were reported
Conclusion: Supplemental IV iron therapy may provide a viable treatment possibly with long-term benefits for some RLS patients. The rapid fall in serum ferritin after the initial 1000 mg dose of IV iron might be seen as reflecting a normal response to this large dose of iron, but the normalization of that fall with repeated doses of IV iron and the correlation of the rate of decline in ferritin with duration of treatment benefit both suggest that this rapid decline represents a pathological state associated with RLS. Moreover, the repeated IV iron leading to a normalization of the ferritin decrease may be correcting a basic abnormality in iron regulation in RLS patients.

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Case Management of 64 Patients with Moderate to Severe Restless Legs Syndrome

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Introduction: Pharmacologic trials demonstrate the efficacy of individual dopamine agonists (DA) in approximately 50-60% of RLS patients. Clinical practice often results in combination therapy that involves multiple CNS agents to improve sleep, wakefulness, mood, dysesthesia, and motor restlessness. The goal of this project is to describe an extended case series/course of patients with restless legs syndrome to assist clinicians in the care of RLS patients.
Methods: Chart review was completed on consecutive new RLS patients seen by the first author between January 1, 2000 and June 30, 2002. Of the 138 patients who met the four-item IRLSSG criteria, 64 had been regularly followed for 15 months or longer. Assessment was then made of the clinical global impression/change; patient ratings of RLS, insomnia, and daytime dysfunction (see DSDQ, Sleep Research 25, 1996, p 197); and the therapeutic interventions at initial visit, three months, six months, and 15+ months.
Results: Of the 64 RLS patients, 93% had primary RLS in 40 females [age: 53.9 (14.2) years; RLS onset: 41.1 (20.6) years] and 24 men [age: 62.7 (11.2) years; RLS onset: 45.9 (17.6) years]. Initial clinical global rating was moderate to very severe in 74% of patients, but at 15 months 81.7% of patients were much or very much improved. 6.8% showed worsening secondary to augmentation. Initial RLS symptom frequency was three or more days a week in 94% of patients. At final visit 71.9% of patients had less than three days per week of symptoms. Significant reduction in patient's ratings of sleepiness/fatigue, RLS/insomnia, and ESS were noted ($p<0.05$). Initial therapeutic interventions included 52 patients receiving DA (34 = pramipexole, 11 = ropinirole, 14 = levodopa), 31 supplemental hypnotics, 20 on antidepressants, 9 on opiates, and 7 on gabapentin. At 15-month visit, combination therapy included 39 patients on pramipexole, 20 taking ropinirole and 3 on levodopa (12 more on prn levodopa) plus 32 using hypnotics, 10 on opiates, and 7 on gabapentin. Over 15 months, four patients had no medication changes, 42 had one to six therapeutic changes and 18 had seven or more changes. After three months, treatment was fairly stable. For example, pramipexole alone was taken by only 9 patients, while 22 took it in combination with other agents (hypnotic n = 14, levodopa n = 4, gabapentin n = 2, or opiate n = 4).
Conclusion: To effectively manage RLS and sleep complaints, clinicians must utilize multiple agents to improve the function and satisfaction of patients. DA alone will optimally treat 20-35% of moderate to severe RLS patients. Combination therapy, particularly with a hypnotic, enhances outcome in half of RLS patients. Antidepressants were continued in 20 of 64 patients. Although the first author commonly sees difficult patients, somnologists should expect to manage increasing numbers of challenging RLS patients.

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Periodic Leg Movements in Congestive Heart Failure

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Introduction: Periodic leg movements in sleep (PLMs) are repetitive movements typically occurring in lower extremities characterized by

dorsiflexion of the foot and knee-flexion. The clinical significance of PLMs is controversial. PLMs are associated with elevated heart rate response and may be associated with daytime somnolence in subjects suffering from congestive heart failure. The prevalence of PLMs in consecutive sample of CHF patients is not well established. The purpose of this study was to: 1. determine the prevalence of PLMs in CHF, 2. characterize sleep in CHF patients with and without PLMs; 3. evaluate heart rate response to periodic leg movements in NREM sleep in subjects with CHF.

Methods: Seventy-nine consecutive subjects followed at the heart failure clinic, Heart Institute, University of Sao Paulo, Brasil were investigated with overnight polysomnography (EMBLA: EEG, EOG, submental EMG, airflow, snoring, respiratory effort, EKG and anterior tibialis EMG). All subjects had ejection fraction (EF) by echocardiography of 50 % or less. Height, weight and Epworth Sleepiness Scale scores were obtained. PSG was scored according to R&K criteria. PLMs were scored manually according to the following criteria: at least four consecutive movements, 0.5 - 4.0 seconds in duration, 5-90 seconds apart. PLMs associated with arousals during ventilatory phase of periodic breathing were excluded. Arousals were scored according to the ASDA criteria. PLMs index (PLMI > 5) was thought to be significant. Heart rate analysis was performed in 8 subjects with PLMs. Heart rate was determined from R-R interval for 10 seconds before and 10 seconds after each of 10 consecutive PLMs in NREM sleep. Statistical analysis was performed using t-test and Mann-Whitney Rank Sum test. The study was approved by the local ethics committee; all subjects provided informed consent

Results: Seventy-nine subjects (51 males, age 59.2 ± 11.4, BMI 25.8 ± 4.9, Epworth 10.7 ± 5.7, EF 35.5 ± 6.0%) were enrolled. None of the subjects were taking anti-depressants. PLMI >5 was present in 13 subjects (16.7%). Subjects with and without PLMs were similar in sex, weight, AHI, central AHI, and ejection fraction, but those with PLMs were older (68.5 ± 10.1 vs. 57.6 ± 10.8, p=0.009). There was no difference between groups in subjective somnolence (Epworth 10.7 ± 5.2 vs. 10.6 ± 5.9; p = 0.48) or in sleep architecture. There was a small but significant increase in heart rate after PLMs (78.6 ± 10.5 vs. 80.1 ± 9.4; p=0.0003).

Conclusion: Periodic leg movements during sleep affect 16.7% of patients with heart failure. Congestive heart failure patients with PLMs and without PLMs are similar in sex, BMI, AHI and ejection fraction, but PLMs patients are older. There is no difference in subjective somnolence or sleep architecture between those with and without PLMs. PLMs in NREM sleep are associated with small but significant elevation of heart rate.

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Mimics of the Restless Legs Syndrome Can Often Satisfy the Standard Diagnostic Criteria

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Introduction: Epidemiological studies have suggested that a large fraction of the population, from 5 to more than 20%, have symptoms of the restless legs syndrome (RLS). Recently, it has become a concern that the positive predictive value of many questionnaire screens for RLS may be fairly low and that many individuals who are identified by these screens have mimic conditions. We have been conducting a family case-control study of RLS with telephone interview of relatives. In the course of this, we have generated information about those who respond positively to screening questions, but do not have RLS. We have now explored our data to find which individuals have mimics that screen positive and how frequently they do so.

Methods: Family members of both RLS definite and control RLS negative probands are contacted. Family members are interviewed blindly by an RLS expert (WAH) using the latest version of a structured telephone diagnostic interview (TDI) with previously demonstrated validity. Besides questions on key diagnostic features of RLS, the TDI contains open ended questions on symptom quality and relief strategies and several additional questions to probe the character of provocative situations and mode of relief. Cramps are explicitly queried.

Results: 96% of 275 family members questioned admitted to having cramps, but only 8 reported both leg discomfort at rest and an urge to move. 6 were asked about other features of RLS and 4 satisfied all diagnostic criteria. But given the very high prevalence of cramps, this might support up to 2% of the entire population satisfying RLS diagnostic criteria because of leg cramps. A subset of 127 family members were determined to have conditions other than RLS as a cause for endorsing some RLS symptoms; 13 satisfied all diagnostic features (10.2%). These had other conditions including cramps, positional discomfort, hypnic jerks, and local leg pathology. Overall, 496 family members were determined not to have RLS by TDI. Over half endorsed at least one RLS feature; 38 satisfied all diagnostic criteria (7.8%), sometimes by responding to different criteria on the basis of differing conditions.

Conclusion: A variety of conditions, including cramps, positional discomfort, and local leg pathology can provide mimics of RLS, and satisfy all diagnostic criteria. In sum, this could amount to several percent of the total population. Definitive diagnosis of RLS requires exclusion of these mimics. In the absence of a more specific screening questionnaire, adequate specificity (and positive predictive value) requires a more comprehensive confirmatory tool such as the TDI or an expert diagnostic interview.

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Circadian Rhythm Of RLS Symptoms: Relationships With Salivary Melatonin, Core Body Temperature And Subjective Vigilance

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Introduction: One of the major characteristics of restless legs syndrome (RLS) is the worsening of symptoms in the evening and/or during the night. Several factors may contribute to the specific distribution of RLS symptoms severity across the 24 hours. Recently, two studies used modified constant routine protocols to investigate the circadian pattern in the occurrence of RLS symptoms. These two studies suggested that RLS symptoms intensity may be modulated by a circadian factor. The aim of the present study was to evaluate nycthemeral or circadian variations in both leg discomfort and periodic leg movement (PLM) in patients with RLS and in matched healthy controls. These variations were then compared with those of 2 well-defined markers of endogenous circadian rhythmicity, namely: core body temperature and melatonin secretion rhythms. Vigilance measures were also included to verify whether the fluctuations in vigilance levels were directly associated with similar fluctuations in RLS symptoms severity.

Methods: Seven patients (3 men and 4 women; mean age + SD: 43.9 + 15.7 years) and seven normal subjects matched for gender and age (mean age + SD: 42.4 + 14.9 years) participated in the study. The experimental protocol started at 11:00 pm and consisted of a 8-hour PSG sleep recording followed by a 25 h modified constant routine protocol divided

into 14 episodes of 2 hours. At all times, ambient lighting was kept below 15 lux measured at eye level. Symptoms severity was assessed by the Suggested Immobilization Test (SIT) administered every 2 hours throughout the constant routine protocol. Subjective vigilance was assessed by the subjects every hour on a 100-mm visual analog scale. Core body temperature was measured every minute by a Mini-Logger monitor. Twenty-eight saliva samples were collected. Melatonin concentrations were determined by radioimmunoassay with a 125-iodine-labeled tracer (Buhlmann Laboratories, Basel, Switzerland). Circadian parameters (acrophase and amplitude) for SIT MDS, SIT PLM index, subjective vigilance, core body temperature and salivary melatonin were estimated with cosinor analyses. Two-way ANOVAs with one dependent factor (group) and one repeated measure (time) were performed to evaluate between-group differences for all variables listed above.

Results: Although the symptoms were more severe in patients than in controls, a significant circadian variation in leg discomfort and PLM ($p<0.01$) was found for both groups. In both groups, the profiles of leg discomfort and PLM were significantly correlated with those of subjective vigilance, core body temperature and salivary melatonin. However, among these variables, the changes in melatonin secretion were the only ones that preceded the increase in sensory and motor symptoms in RLS patients.

Conclusion: These results and those of other studies showing that melatonin exerts an inhibitory effect on central dopamine transmission suggest that melatonin might be involved in the worsening of RLS symptoms in the evening and during the night.

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Nocturnal Quiescegenic Dyskinesia (NQD): A Newly Recognized Sleep-Related Movement Disorder Sometimes Confused With The Restless Legs Syndrome

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Introduction: The diagnostic criteria for the restless legs syndrome (RLS) developed at a consensus workshop at NIH and approved by the International Restless Legs Study Group requires the patient experiences a feeling of an urge to move the legs. The sensation of the urge to move defines the disorder rather than the occurrence of movement. This has been described by some as a focal akathisia, rather than any abnormal movement or dyskinesia per se. Many RLS patients, however, experience nocturnal dyskinesias characterized as involuntary leg movements, often abrupt leg jerks. Such nocturnal movements are frequently attributed to RLS. We, however, observed that some patients referred for RLS evaluation had nocturnal involuntary leg jerks typical of RLS which met all of the diagnostic criteria for RLS except there was no urge to move nor other sensation associated with the movements. We were interested in characterizing these patients and determining their similarity to RLS patients.

Methods: The diagnostic codes for our patients were modified to specifically include one for the patient with nocturnal involuntary leg jerks brought on by rest and relieved with movement but without any sensation or urge to move associated with the leg movements. We reviewed the charts of all patients prospectively given this diagnosis first to ensure the clinical reports matched the diagnostic criteria and second to characterize these patients. The diagnosis required: repeated involuntary leg jerks engender by waking rest, relieved by leg movements (usually walking) and worse in the evening or night. The relief by movement criteria required that the patient reported initiating moving or walking in order to stop the involuntary leg movements. Sleep starts were excluded by the requirement that these were repetitive while resting and not occurring only during the sleep onset time. The clinical cases of all patients identified as meeting these criteria were reviewed provided all appropriate releases for research use of medical information had been obtained from the patient.

Results: Twelve patients were identified (4 female, 8 male); ages 31 to 91, average 60.5. Age of reported onset of symptoms varied from 25 to 76, average 50,2. Symptoms started before age 45 for 4 and before 40 for 2. Polysomnograms obtained on 5 showed PLMS/hr of 16 to 111 (average 62.7). All patients reported a fairly abrupt onset of symptoms and 2 reported occurrence after surgery and 1 after a severe flu-like illness. Progression from nighttime only to evening occurred for 6 and was rapid (within 2 years) for 3 patients. One and only 1 other member of the family had RLS for 2 of the 10 with family history information. Seven of the 12 patients had neurological abnormalities: 1 with a slowly progressive gait imbalance developing after these symptoms started, 1 with multiple myeloma, 1 with axonal demylinating polyneuropathy, 3 with only decreased vibratory sensation and decreased or absent ankle reflexes with some mild numbness, and 1 with well documented chronic fatigue. Two had mildly low iron stores; one treated with oral iron showed no clinical response. Dopaminergic treatment tried in 9 produced satisfactory improvement in 7, no change in 1 and worsening of symptoms in 1 patient.

Conclusion: NQD patients differ from RLS patients. Their symptoms generally started after age 40. The familial prevalence of RLS was no greater than expected by chance indicating no familial relation between NQD and RLS and no family history of NQD. These characteristics somewhat match late-onset (over age 45) RLS. However, unlike late-onset RLS, most NQD patients had other significant neurological disorders contributing to their condition and dopaminergic treatment was effective in only 77% of the cases. Further consideration of this sleep-related movement disorder may inform about factors contributing to these circadian and rest engendered involuntary leg movements.

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A Single-Blind, Placebo-Controlled, Forced-Titration Study of Ropinirole in RLS: Pharmacokinetic-Pharmacodynamic Relationships

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Introduction: The efficacy of ropinirole in RLS (Ekbom syndrome) has been well established in large clinical trials. This trial (protocol: 101468/218) was designed to assess the pharmacokinetics of ropinirole in patients with RLS. A secondary objective was to investigate whether there was a relationship between systemic exposure to ropinirole and changes in efficacy parameters.

Methods: A total of 28 patients with primary RLS were randomized to receive ropinirole (n=18) or placebo (n=10). The ropinirole dose was uptitrated using a standard regimen from 0.25 to 4.0 mg/day, in a forced manner, if tolerated. Blood samples were collected for pharmacokinetic analysis at four of the eight dose levels, according to an incomplete block design. Efficacy analyses were based on the International Restless Legs Scale (IRLS) and on periodic leg movements in sleep (PLMS), recorded by actigraphy. Response on the IRLS was defined as a greater than 6-point reduction in IRLS score from baseline. Response on PLMS criteria was a greater than 50% reduction in the number of PLMS per hour (PLMS/hour) in the night.

Results: For the IRLS, there was a clear trend for the proportion of responders to increase with increasing systemic exposure to ropinirole; the proportion increased from ~30% in patients receiving placebo to 80% in patients with higher exposure (AUC0-24) to ropinirole. Logistic regression predicted that 50% of patients would be responders, based on

the IRLS, at AUC0-24 values of ~20 ng.h/ml, whereas 80% would respond at a value of ~45 ng.h/ml. These exposures correspond to ropinirole doses of 1.0-2.0 and 3.0-4.0 mg/day, respectively. For PLMS, there was again a clear trend for the proportion of responders to increase with increasing overnight systemic exposure to ropinirole. This increase reached a plateau at responder rates of ~70% in all patients studied, and ~80-90% in patients with ≥ 10 PLMS/hour at baseline. Logistic regression predicted that 50% of patients would respond on PLMS at an AUC0-12 value of ~20 ng.h/ml, which corresponds to a ropinirole dose of 2.0-2.5 mg/day. For patients with ≥ 10 PLMS/hour at baseline, a 50% probability of response was associated with exposure values of ~10 ng.h/ml, which corresponds to a dose of ~1.0-1.5 mg/day. As expected with a forced-titration regimen, the incidence of adverse events was high. Nausea was the most common, with 95% of episodes being mild or moderate in severity and 54% starting on the first or second day of a new dose level. For spontaneously resolving nausea episodes with recorded start and stop times, 93% lasted less than 24 hours and 59% lasted less than 2 hours.

Conclusion: An exposure-response relationship was found for ropinirole when response was based on reductions in either the IRLS score or PLMS/hour. Based on a logistic model, and taking into account pharmacokinetic variability, 50% of patients were predicted to respond on either parameter at doses of ropinirole greater than 1.5 mg/day.

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Exploring Ferritin Levels from an Age- and Gender-Matched Primary Care Population of Patients with and without Symptoms of RLS

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Introduction: The Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness about sleep disorders and to determine their prevalence within a primary care practice in Moscow, Idaho. Data gathered by our group during a one year period from December 1999 to December 2000 documented that 24.0% (504/2,099) of the patients within the Moscow Clinic population had symptoms of Restless Legs Syndrome (RLS) at least occasionally. These preliminary RLS diagnoses were based on a validated questionnaire, the RLS Questionnaire (RLSQ). The RLSQ includes questions related to each of the four diagnostic criteria established by the International RLS Study Group (IRLSSG).

Methods: For a one-year duration, each patient with an appointment at the Moscow Clinic was asked to complete the RLSQ. The questionnaire was completed by 79.2% (2,099/2,649) of the adult population. All patients with an RLSQ Positive questionnaire and a predetermined (and randomly selected) number of patients with an RLSQ Negative questionnaire were asked to participate further. Further participation involved a blood draw to measure ferritin levels, an interview by the patient's primary care physician, and the completion of ten additional questionnaires. A total of 297 patients completed the additional components. The results from the physicians' interviews have been reported previously. This abstract describes a subgroup of RLSQ Positive patients from this study who have been age- and gender-matched to RLSQ Negative patients. The purpose of these analyses was to look for differences in the ferritin levels. From the primary care population, 59 matched pairs were formed. Further analyses were performed for this particular subgroup.

Results: Upon evaluation of the matched pairs (Mean Age ± SD, RLSQ Positive: 46.6 ± 17.7, RLSQ Negative: 44.5 ± 19.4; M/F: 19/40), it was determined that the mean ferritin level for RLSQ Positive patients was significantly lower than the mean ferritin level for the RLSQ Negative patients (80.9 ng/ml vs. 102.5 ng/ml; $t=1.86$, $p<0.03$). Further, The RLSQ Positive patients had significantly higher scores on the Epworth Sleepiness Scale (7.8 vs. 6.3; $t=-2.22$, $p<0.02$) and the Beck Depression Inventory II (11.5 vs. 8.3; $t=-1.92$, $p<0.03$). There was not a significant difference in body mass index between the two groups (26.7 vs. 26.4; $t=-0.31$, $p<0.38$).

Conclusion: Our results from this primary care sample indicate that patients with symptoms of RLS (RLSQ Positive) tend to have a lower ferritin level than patients who do not report RLS symptoms (RLSQ Negative). Further, those with RLS symptoms tend to score higher on the ESS, which indicates an increased level of daytime somnolence, and the BDI-II, which indicates an increased level of symptoms related to depression. It is likely that the sleep deprivation that is characteristic of individuals inflicted with RLS may be related to the increased level of subjective sleepiness. The increase in depressive symptoms may stem from a number of factors: sleep deprivation, a reduced subjective quality of life that has been previously correlated to individuals with RLS, or other factors related to the fact that these subjects were recruited from a primary care practice.

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"External Counter Pulsation (ECP)" A Novel Non Pharmacological Treatment For Restless Legs Syndrome (RLS)

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Introduction: External Counter Pulsation (ECP) is used in patients with angina refractory to medical therapy and who are not readily amenable to surgical intervention. Patients are treated with ECP one hour a day, five days a week for seven weeks for a total of 35 hours. ECP involves inflation and deflation of 3 sets of compressive cuffs wrapped around the patients calves, lower thighs and upper thighs. During diastole the cuffs inflate sequentially from the calves to the upper thighs and buttocks to raise diastolic aortic pressure and increase coronary perfusion pressure. ECP increases venous return and collateral flow to ischemic regions of the myocardium and decreases left ventricular work load. ECP also compress the vascular beds of the legs which increases venous return. We found some patients who underwent ECP who also had severe Restless Legs Syndrome (RLS) who coincidentally showed significant improvement in RLS symptoms. We therefore decided to try a more formal trial of ECP in patients with cardiovascular disease who also have RLS.

Methods: We found five patients(1F,4M,ages 60-80) who have been identified as candidates for ECP treatment. Four patients had refractory angina and one had congestive heart failure. None of these patients had significant leg edema. All five of them had clinically significant RLS and they were not treated for RLS. Two of these patients were on Neurontin for back pain, but the dose remained stable throughout the study. All patients were given the International RLS Study Group rating scale for RLS (the IRLS) before and immediately after 35 days of ECP treatment. We also administered the IRLS to 2 patients 3 months and 8 months after completing the ECP treatment.

Results: The average IRLS rating scale score before treatment was 29.2 and after 35 days of ECP was 7.2 (P<.001). Two of these RLS patients had 100% symptomatic improvement with a severe initial IRLS score of 28 and 26 that decreased to zero after the 35 days of ECP treatment. They had symptoms present for 9 and 23 years respectively that occured 4-5 times per week. One of these patients was totally asymptomatic for the 3 months after ECP and remained with an IRLS score of zero. A third patient's IRLS score decreased from 23 at baseline to 4 after 35 days of ECP. He was also totally asymptomatic for the 8 months after ECP and the IRLS score was zero. This patient also reported symptoms since childhood that occured 6-7 times per week. A fourth patient had an IRLS score of 34 prior to treatment that went down to 5 after ECP. The fifth patient had an IRLS score that only went down from 35 to 27 after 35 days of ECP. However, this patient did not find much improvement in cardiac symptoms either and requested another course of treatment. One of our 5 patients who had an initial IRLS score of 26, came back for repeat ECP because he had experienced sustained improvement of RLS for more than a year after his first ECP. All 4 patients reported improved sleep and RLS significantly.
Conclusion: External Counter Pulsation improves RLS symptoms significantly and it could be considered as an adjunct treatment in patients with RLS who qualify for ECP. The IRLS scores showed a 22 point drop after ECP which is far more than the placebo response of 8 points seen in trials of pharmacotherapeutic agents for RLS. The improvement also lasts for months after the last treatment. In this way ECP is unique and unlike pharmacotherapy which requires continuous daily treatment. Furthermore, our results suggest that changes in vascular flow influence the peripheral or central nervous system leading to the sensory symptoms of RLS. This is probably true independent of the presence or absence of cardiac disease since some of our patients had RLS since childhood or young adulthood long before the onset of heart disease. We need a larger number of patients with accompanying Polysomnography and Actigraphy to draw further conclusions.

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Does Amplitude Matter in Periodic Limb Movement (PLM) Counts?

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Introduction: Periodic Limb Movements (PLM) during sleep are recorded and scored according to standard criteria developed by Coleman and slightly modified by the American Sleep Disorders Association (Sleep 1993; 16: 748-759). Scoring criteria indicate that tibialis anterior muscle activation in EMG with a burst duration between 0.5 to 5 seconds, an amplitude over 25 % of calibration movements and with an interval of at least 5 seconds and no more than 90 seconds between their onsets, occurring in series of 4 or more LM are counted for PLM. We investigated the relationship between periodic limb movement (PLM) counts obtained with standard scoring criteria and PLM counts scored according to the same criteria except the amplitude criterium in a mixed sleep disorder population.
Methods: 24 patients (mean age 57.5 +/- 12.0 years) with a PLM index (PLMI) > 5 per hour in a previous polysomnography (PSG) underwent a full night (8 hours) of digital PSG (Schwarzer Brainlab, Munich, Germany). PLM were recorded and manually scored according to standard criteria manually for time in bed (TIB), NonREM and REM sleep. PLM in wakefulness were scored with a maximum duration of 10 seconds (Michaud 2001). In a second step we counted PLMS without the amplitude criterium for the same subjects and the same nights and compared the PLM counts obtained with both methods.
Results: The periodic limb movement index (PLMI) was 34.4 +/- 30.7 PLM/hour (h) and 50.2 +/- 36.4 PLM/h with / without amplitude criterium (AC) for TIB. This difference was statistically significant (p<0.001, paired t-test). The PLMI with / without AC in NonREM sleep was 27.5 +/- 24.3 and 38.5 +/- 28.4 (p<0.001, paired t-test), in REM sleep 1.5 +/- 2.7 and 3.7 +/- 5.0 (p=0,005, paired t-test) and in wakefulness: 5.4 +/- 9.4 and 7.9 +/- 11.7 (p<0.001, paired t-test).
Conclusion: In comparison to PLM counts obtained with strict application of standard criteria, PLM counts obtained without consideration of the amplitude criterium are remarkably higher. This may relate to the fact that counting without AC increases the sensitivity to detect single LM, and allows for identification of PLM sequences which would not have fulfilled the periodicity criteria otherwise. The strict application of the amplitude criterium is difficult as instructions are mainly qualitative. Moreover the amplitude criterium is an arbitrary variable and its clinical significance is uncertain. Further studies should determine, if PLM counts without AC are more useful to detect the activity of the periodic oscillator underlying PLM.

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Changes In Prolactin Response To L-Dopa During Long Term Dopaminergic Treatment In Restless Legs Syndrome Augmentation

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Introduction: RLS augmentation is a frequent complication of long-term treatment with dopaminergic drugs and reflects an overall worsening of Restless Legs Syndrome(RLS) symptoms during treatment. The pathophysiology of RLS augmentation remains unknown. Nevertheless, it has been suggested that it could be related to long-term dopaminergic treatment induced changes in dopamine receptor sensitivity. The objective of this study was to investigate, by means of a neuroendocrine challenge, a possible relation of RLS augmentation to changes in dopamine receptor sensitivity.
Methods: Fourteen previously untreated patients with idiopathic RLS were treated for 12-15 months (mean: 14,1 months) with L-DOPA. The mean dosage was 191 mg/day. Severity of symptoms was evaluated every two months by means of the International RLS scale (IRLS). A blind rater evaluated patients regarding presence (AUG) or absence of augmentation (N-AUG). In addition, patients underwent before and after treatment a suggested immobilization test (SIT) followed by a sleep study. On the following day, patients underwent at 23:00 an L-DOPA neuroendocrine challenge: After insertion of an iv line, 400 mg L-DOPA (+50 mg carbi-DOPA) were administered orally at 2300. Blood was drawn 20 and 5 minutes before administration of the drug, as well as 15, 30, 45, 60, 75, 105 and 120 minutes after, and analyzed for plasma values of PRL. A group of thirteen age- and gender-matched healthy controls underwent at baseline also the SIT, the sleep study and the neuroendocrine challenge. Hormonal assays were performed blindly to diagnosis, treatment outcome or augmentation status.
Results: a. Six men and eight women were included in the sample, with a mean age of 59,2 years (+3,5). The mean (SD) IRLS-score improved during treatment from 26,1(4,1) to 12,1 (3,2) points (p<0.05). Six out of the fourteen patients were classified as AUG. b. In both RLS and control groups, baseline PRL plasma levels decreased following acute administration of L-DOPA. However, the reduction (measured as area under the curve-AUC-) was more pronounced in RLS than in controls (p<0,05). c. Following long term dopaminergic treatment, PRL was less inhibited by acute administration of L-DOPA than before treatment in the AUG group (p<0,05) but not in the N-AUG group. d. No statistical differences were found between PRL response to L-DOPA following long term treatment in AUG and controls.

Conclusion: The results suggest a mild decrease in dopamine receptor sensitivity in RLS patients experiencing augmentation during long term treatment with L-DOPA. We propose that a loss of therapeutic efficacy due to a reduction in postsynaptic dopamine receptor sensitivity during long-term dopaminergic treatment might be involved in the pathophysiology of RLS augmentation.

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Parkinson Disease Sleep Scale (PDSS): Measuring Disease Specific Nocturnal Symptoms In PD Patients

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Introduction: Sleep disturbances may occur in up to 96% of patients with Parkinson disease (PD) and appear to arise from a combination of neurodegenerative and neuropharmacological changes in central sleep regulation such as the forebrain, thalamus and midbrain dopamine (DA) neurones. Recent surveys have indicated the importance of sleep disturbance in determining the quality of life of PD patients. The Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and the Unified Parkinson Disease Rating Scale (UPDRS), the gold standard to assess the severity of PD, do not systematically address and quantify the different aspects of sleep disturbance in PD. We have therefore developed a 15-item visual analogue scale for comprehensive assessment of the symptoms contributing to sleep disturbance in PD, the PDSS, and validated the scale (Chaudhuri et al 2002).
Methods: The PDSS is a visual analogue scale (VAS, 0 = very bad, 100 = excellent) addressing 15 commonly reported symptoms associated with sleep disturbance in PD(i.e. addressing nocturnal akinesia, early morning dystonia, REM sleep behaviour disorder, nocturnal hallucinations and others). The PDSS total score is defined as the mean of all 15 VAS ratings. We report here data from a comparative, randomized, double-blinded, cross-over study with two dopamine agonists to measure the usefulness of the PDSS in treatment trials. The PDSS was used in a 20-week study comparing two dopamine agonists in patients with PD and nocturnal akinesia using the PDSS as primary outcome measure. 28 levodopa-treated patients (Hoehn and Yahr stage I-IV) with nocturnal sleep disturbance and a non-sufficient control of their motor symptoms during daytime. Treatment period was 20 weeks with a wash-out period of one week and a cross-over period of 2 weeks. UPDRS and PDSS scores were assessed at baseline, at the end of crossover period I after 12 weeks, and of crossover period II after 20 weeks of treatment.
Results: Of 28 patients (mean age 69 years, 54% females), 23 were evaluable with respect to the rating scales. PDSS total score at baseline indicated moderate impairment of sleep (mean = 48.7); by endpoint, a mean improvement of 28% was seen in the pooled treatment groups. Treatment differences were observed in five PDSS items ($p<.05$) and in further three items, a tendency ($p<.10$) for treatment differences was noted. Slight, but not significant improvements in the UPDRS Item 31 (question on quality of sleep) were comparable in both treatment groups.
Conclusion: The PDSS is a simple, validated self-rating measure to assess the subjective sleep quality in PD patients. Sensitivity for treatment differences was demonstrated in this trial and it may therefore be considered in treatments trials. Compared with the UPDRS (one question), the PDSS can further differentiate between the factors contributing to the sleep problems in PD patients and therefore enhance quality of treatment regimens in PD patients with sleep disorders.

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Subclinical Restless Legs Syndrome In People Who Came Up To Sleep Check-Up Clinic

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Introduction: Insomnia is not a required symptom for making a diagnosis of RLS according as standard RLS definition criteria, therefore, the prevalence of RLS may not reflect the population of RLS patients who need medical assistance. However, such patients are less likely to ask for consultation and we do not know much about clinical characteristics of these patients.
Methods: Consecutive 504 people (mean age 51.6, SD=13.5, 390 men and 114 women) who came to sleep check-up clinic in our center between Nov 2001-Nov 2003 was examined after having a comprehensive health and sleep questionnaire. The questionnaire included questions asking major RLS symptoms (1-unpleasant sensation, 2-motor restlessness, 3-motor relief, 4-nocturnal worsening) and the Insomnia Severity Index (ISI). On consultation, we checked the questionnaire of all cases, and tried to rule in and out the diagnosis of RLS by taking a detailed history. The ISI total score of them was calculated to quantify perceived insomnia severity.
Results: Twenty-six people (5.2%) was diagnosed as having RLS, and the mean ISI total score of them was 10.2 (SD=7.2) including eight people who scored 15 or more. Three out of 26 had come to our clinic due to solely difficulty initiating sleep associated with leg discomfort (ISI=22, 14, and 21, respectively). There were another three people with a complaint of insomnia (ISI=18, 19, and 20, respectively), but one came for consultation because of self-suspected sleep apnea-hypopnea syndrome, and the other two had been already treated elsewhere with diagnoses of depression and psychophysiologic insomnia, respectively. Although these three insomniac patients fulfilled the RLS definition criteria, they did not attribute their insomnia to RLS, because their RLS core symptoms were mild and infrequent, and/or their insomnia had occurred before noticing RLS symptoms. The rest of these 26 people came mostly because of heavy snoring and witnessed apnea and they had not mentioned RLS symptoms spontaneously in response to our open-ended questions (e.g. What is the trouble about your sleep?) until we pointed out them based on answers that they had made on the questionnaire. They regarded their sensory/motor symptoms as non-pathological, as they were mild and/or infrequent.
Conclusion: RLS seems to have a wide severity spectrum and there may be a certain population that could be considered having subclinical RLS. Longitudinal follow-up study is necessary for knowing whether these cases will develop full-blown RLS or remain mild for a long time.

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Periodic Limb Movements Syndrome in Patients with Severe Obstructive Sleep Apnea Treated with Continuous Positive Airway Pressure

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Introduction: Obstructive sleep apnea syndrome (OSAS) is frequently associated with periodic limb movements syndrome (PLMS). Moreover continuous positive airway pressure therapy (CPAP) can provoke or intensify PLMS particularly in patients with severe OSAS. In turn PLMS by itself can lead to significant sleep fragmentation and decrease of the quality of CPAP treatment. The objective of the study was to determine the prevalence and clinical significance of PLMS in patients with severe OSAS during the first night of CPAP treatment and during

the follow-up polysomnography (PSG) after 1 month of CPAP-treatment.
Methods: We retrospectively analyzed 98 consecutive patients with severe OSAS, apnea+hypopnea index (AHI) >40, mean AHI = 64.5±8.8, 90 men and 8 women, mean age 54.3±7.9 years. Diagnosis of OSAS was made by all-night full polysomnography (PSG). All patients were treated with CPAP under the control of PSG at the following night. PLM and PLM associated with arousal (PLM-A) were scored according to ASDA criteria (ASDA and Atlas Task Force 1993). The follow-up PSG was made in 12 patients with severe PLMS (PLM > 50) after 1 month of CPAP treatment.
Results: It was very difficult to distinguish PLM and movement activity connected with OSAS particularly in patients with severe OSAS. So it was impossible to evaluate the frequency and severity of PLMS in our patients before CPAP treatment. During the first night of CPAP treatment the mean PLM index was 49.8±19.3. PLM index greater than 5 was found in 62 patients (63.2%). The severe PLMS (PLM >50) was found in 16 patients (16.3%). In that group the mean PLM index was 94.2±22.5, the mean PLM-A index was 32±14.3. It led to significant deterioration of sleep micro- and macrostructure and decrease of subjective quality of CPAP treatment. In 12 out of 16 patients with severe PLMS the follow-up PSG was made after 1 month of CPAP treatment. The mean PLM index dropped from 91.3±24.9 to 21.4±15.4 ($p<0.0001$).
Conclusion: PLMS is frequent during the first night of CPAP treatment in patients with severe OSAS. In some patients PLMS can be severe, which in turn deteriorates the sleep quality and can lead to lack of clinical effect during the first night of CPAP treatment. Severe PLMS diagnosed during the first night of CPAP treatment in the patients with severe OSAS appears to be self-limited and does not require any specific treatment.

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Efficacy of Graduated-Dose Levetiracetam in Treating Restless Legs Syndrome and Associated Hypersomnia: A Pilot Study

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Introduction: Restless Legs Syndrome [RLS] is a sleep and neurological disorder characterized by unpleasant sensations in the limbs, triggered by inactivity and relieved by movement. It is associated with difficulty falling asleep, and most patients have periodic limb movements [PLMS] during sleep, often resulting in daytime hypersomnia. Faulty dopamine utilization, CNS iron deficiency, comorbid sleep and medical disorders, pregnancy, and certain medications have been associated with or trigger RLS. Familial forms exist as well. Iron supplements, dopamine agonists, levodopa, analgesics, anticonvulsants and behavioral therapy have been used as treatment with varied success. The MOA of levetiracetam [Keppra] hasn't been fully characterized, though calcium channel [N-type] inhibition and indirect GABAergic modulation may contribute to its activity.
Methods: 10 subjects [ages 35-81 yrs; 6 female, 4 male] with RLS and hypersomnia diagnosed by a sleep expert were entered into an open label protocol. Levetiracetam was given as a single dose taken 3 hours before bedtime according to the following schedule: 500 mg for two weeks, then 1000 mg for two weeks, then 1500 mg for two weeks. Assessment tools utilized were the International Restless Legs Study Group [IRLSSG] questionnaire, the Epworth Sleepiness Scale, and the Clinical Global Impression of Change [CGIC] scale- administered at baseline, 2 weeks, 4 weeks, and 6 weeks/study termination. Exclusions were for major comorbid medical or psychiatric disease, pregnancy or levetiracetam allergy. Any RLS medications were stopped two weeks prior to starting the study.
Results: 7 of 10 patients completed the study. Of the completers, mean IRLSSG scores fell from 26.07 [baseline] to 18.42 [end of 500 mg arm] to 16.14 [end of 1000 mg arm] to 13.71 [end of 1500 mg arm], scale rated as 26-40 severe, 16-25 moderate, and 1-15 mild. Epworth Sleepiness Scale fell from 8.28 baseline to a low of 6.28 [seen at the end of the 1000 mg arm]. 6 of 7 subjects rated themselves as therapeutically improved on the CGIC scale. Of the non-completers, one dropped out for palpitations [unrelated to drug- had prior history]; two others dropped out due to sedation- one in the 500 mg arm and one in the 1000 mg arm. Both reported their RLS symptoms as improved before dropping out.
Conclusion: We believe this preliminary study suggests a significant role for levetiracetam in the therapeutic armamentarium for RLS. A second study using these scales, an additional lower initial dosing arm to minimize sedation, and with serial polysomnograms for PLMS assessment is to begin shortly. Though a large, double-blind study is required for firm conclusions and statistical significance, this initial data compares favorably to recently published studies using other forms of therapy.

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Restless Leg Syndrome in Rheumatoid Arthritis

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Introduction: Authors studied the occurrence of Restless Leg Syndrome (RLS) in patients with rheumatoid arthritis (RA). The significance of iron deficiency and peripheral neuropathy associated with RA in the development of RLS is reviewed. The correlation of patients iron status and the severity of RLS symptoms is assessed. It is maintained that iron deficiency, with or without anaemia, plays an important role in the development of RLS symptoms. Rheumatoid arthritis and Sjogren syndrome were diagnosed in 25% of the secondary forms of RLS.
Methods: Nineteen consecutive and non-selective patients with classical RA were studied. To assess the activity of RA, the duration of articular rigidity in the morning and Ritchie index were checked, while pain was assessed by means of a visual analogous scale. Laboratory activity indices (ESR, CRP, RF) concerning iron metabolism (blood count, daytime and night time serum Fe, total Fe-binding capacity, serum ferritin level) were examined. The following investigations were carried out in each patient: RLS questionnaire, Forced Immobilization Test (FIT-test), Actigraphy, EMG/ENG, Polysomnography and sleep diary. Patients: 19 patients with rheumatoid arthiritis were studied. Mean age was 65 years (ranging from 39 to 76 years). There were 3 male and 16 female patients. The rheumatoid disease was clinically active in 8 patients and inactive in 11 patients. The patients were on NSAID, steroid, Methotrexat and Salazopyrin therapy. The patients were split into two groups: (Group A, n=6), where RLS was suspected on the basis of clinical symptoms and the questionnaire, and (Group B, n=13) with no suspicion of RLS.
Results: Inflammation activity parameters: ESR: A:32,5mm/h, SD:6,3 mm/h, B: 54,5mm/h SD:18,8mm/h; RF titer: A:53,3U/ml, SD:19,9 U/ml, B: 289,5V, SD:30,1 U/ml; CRP: A:0,9mg/dl SD:1,44CU/ml, B:1,48mg/dl SD:1,38mg/dl. Iron metabolism tests: SeFe level in the morning: A:8,9umol/l SD:2,8umol/l, B:8,9umol/l SD:2,1umol/l.; SeFe level at night: A:2,4umol/l SD:0,64umol/l, B:5,6umol/l SD:2,4umol/l. Total Fe-binding Capacity: A:63,3umol/l SD:17,6umol/l, B:60,4umol/l SD:9,8umol/l; Serum ferritin level: A: 45,4ug/l SD:13,6ug/l, B: 111,3ug/l SD:40,8ug/l.; FIT test: A: 28,1movements/hour SD:5,9 movements/h, B: 9,7 movements/hour SD:2,6 movements/h, Total Movement

Time/Total Sleep Time: 43,3% SD:6,3%, B: 14,8% SD:3,0%. During polysomnography, arousal index, beginning of sleep, number of sleep stage cycles and effectiveness of sleep were also studied in each patient.
Conclusion: A study of patients with RA revealed, in line with literature data, that secondary RLS occurred more frequently (30%). No correlation was found between inflammatory activity of RA and clinical severity of RLS. Low serum ferritin value (50 umol/l) correlated well in patients with RA with the severity of RLS symptoms and deterioration in the effectiveness of sleep.

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Comprehensive Clinical And Video-Polysomnographic Characterization Of Idiopathic REM Sleep Behaviour Disorder And That Associated With Multiple System Atrophy And Parkinson's Disease

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Introduction: Rapid eye movement (REM) sleep behaviour disorder (RBD) is a common sleep disturbance that precedes and accompanies several neurodegenerative disorders, particularly those which share in common waking motor impairments consistent with parkinsonism such as multiple system atrophy (MSA) and Parkinson's disease (PD). We sought to assess whether unique clinical and electrophysiologic characteristics of RBD might differentiate MSA from PD. In addition, we characterized the idiopathic form of RBD which frequently precedes by several years the waking symptomatology of MSA and PD.
Methods: Demographic and clinical features, and comprehensive audiovisual-polysomnographic (PSG) measures were compared in 151 consecutive subjects presenting with RBD (41 with MSA, 65 with PD and 45 with idiopathic RBD) with extended follow-up (mean 27.9 months).Diagnosis of RBD required not only a long-standing history of vigorous sleep behaviour, but also: 1) audiovisual-PSG confirmation of abnormal motor behaviours during REM sleep; and 2) evidence for tonic and/or increased phasic electromyographic (EMG) activity within PSG-defined REM sleep (Schenck and Mahowald, 2002).
Results: RBD occurring in the setting of MSA could be distinguished from RBD in the context of PD on the basis of being nearly equally common amongst men and women (1.2:1 in MSA versus 2.4:1 in PD), more frequently preceding the waking manifestations of parkinsonism, and occurrence at a younger age. Duration of RBD symptomatology in MSA was longer and characterized by increased amount of stage III-IV sleep, higher percentages of REM sleep without atonia and limb phasic electromyographic activity, and increased periodic leg movements in sleep. Subjects with idiopathic RBD, as compared to those with either MSA or PD, were more frequently male, had greater RBD severity and unpleasant dream recall, were more aware of their abnormal sleep behaviours, and had fewer self-reported sleep complaints, including awakenings. Seven of the 45 subjects initially diagnosed with idiopathic RBD developed parkinsonism and/or dementia during follow-up. Clinical and PSG features could not differentiate between those subjects who developed motor or cognitive deficits and those who did not.
Conclusion: The different sleep-related phenotypes of disease as demonstrated here have important implications for diagnostic accuracy and thereby prognostic determinations, and the future development of appropriate treatment interventions (particularly when RBD is encountered in otherwise asymptomatic individuals). This comprehensive assessment of demographic, clinical and PSG features of RBD in MSA, PD and idiopathic groups, for example, establishes a solid basis from which the pathophysiologies underlying RBD in the setting of, and prior to, neurodegenerative diseases can be further investigated. Differences detected here may have their basis in different indirect or direct effects of disease pathology on brainstem structures that modulate REM sleep, hormonal differences, or the effect of dopaminergic agents on periodic leg movements

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Prevalence Of Restless Legs Syndrome In France And Its Impact - The INSTANT Study

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Introduction: Prevalence of Restless Legs Syndrome (RLS) has been estimated in several Western countries (5% to 15%) but never in France and few studies have measured the impact of RLS for patients in terms of quality of life and quality of sleep. The objective of this study was to estimate the prevalence of RLS in the French adult population and evaluate its impact on quality of life and quality of sleep.
Methods: A population-based survey was conducted among 10 263 adults through face to face interviews by using a stratified sampling method (on age, sex, geographical living area, economic working class and woman working status). The screening was made with the 4 International RLS Study Group (IRLSSG) criteria. RLS severity was estimated with the IRLSSG-Rating Scale. Quality of life and quality of sleep were assessed with the SF-36 and the MOS-Sleep questionnaires among subjects suffering from RLS and among a control group of 540 subjects randomly selected among the global sample of people not suffering from RLS.
Results: 870 subjects have been identified as suffering from RLS within the last 12 months among the 10 263 interviewed. The French annual prevalence of RLS adjusted on age and sex was estimated at 8.5% CI95%=[8.0%; 9.0%].The distribution of RLS sufferers according to the Rating Scale score showed that 16.8% were severe (i.e. from 21 to 30) and 4.4% very severe (i.e. from 31 to 40). Among the RLS population, the sex ratio was 2 women / 1 man .The mean age at first occurrence of symptoms was 35.2 years. After adjustment on age and sex, all SF-36 dimensions and MOS-Sleep dimensions were significantly worse (with $p<0.001$) in the RLS population (especially those having symptoms at least once a week) than in the control group, respectively: 1. Quality of life dimensions (SF-36): - Physical Functioning: 83.2 vs. 87.2 - Role Physical: 75.1 vs. 84.6 - Bodily Pain: 64.5 vs. 75.1 - General Health: 62.7 vs. 69.6 - Vitality: 53.8 vs. 59.6 - Social Functioning: 77.9 vs. 85.2 - Role emotional: 75.1 vs. 84.0 - Mental Health: 62,3 vs. 68,3 2. Sleep dimensions (MOS-Sleep): - Index I: 33.8 vs. 26.0 - Index II: 35.2 vs. 27.3 - Sleep disturbance: 37.9 vs. 28.8 - Sleep adequacy: 53.9 vs. 63.4 - Somnolence: 30.1 vs. 24.3.
Conclusion: RLS affects 8.5% of the French adult population, particularly women (sex-ratio 2/1). This prevalence is consistent with the findings of studies from other western countries. RLS has a significant impact on quality of life and quality of sleep.

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Severity Rating of Restless Legs Syndrome: Validation of the RLS-6 Scales

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Introduction: The RLS-6 scales were applied as efficacy endpoints in several double-blind and open-label trials with dopaminergic drugs for the treatment of patients with a restless legs syndrome (RLS). During the years, the scales have been extended and modified. Results from validation studies with the final version of the RLS-6 scales are presented.
Methods: The RLS-6 scales are six global rating scales each of which is using 11 categories from 0 = "no symptoms" to 10 = "maximum severity of symptoms" for grading. They were designed to evaluate efficacy of RLS treatments by changes between baseline and post-baseline assessments. With four scales, severity of RLS "at bedtime", "during the night", "during daytime when at rest", and "during daytime when engaged in activities" is to be assessed by RLS patients. A further item requests the patients to evaluate their "satisfaction with sleep", and the remaining item asks for severity of "daytime tiredness / sleepiness". All six scales are evaluated separately, no total or sub-scale scores are intended. Psychometric properties of the RLS-6 scales were investigated by factor analysis and intercorrelation of the items. Criterion validity was investigated by correlation to the IRLS and to polysomnographic PLM arousal index (PLMAI). Sensitivity for drug effects was determined by comparison of active therapy and placebo.
Results: Psychometric evaluation was performed with the baseline data (N=259 patients with idiopathic RLS, 57 years of age, 68% females) of a cabergoline study. Mean severity ranged between 1.7 ± 2.2 (severity during the day when active) and 6.7 ±2.6 (impaired quality of sleep). Factor analysis yielded two factors with the two day-time severity items building up one factor and the remaining items the other factor. Mean intercorrelation of the items was r=.37. Correlation between the IRLS total score (mean severity: 25.7 ± 7.0) and the RLS-6 scales was highest to "severity during the night" (r=.69) but markedly lower to the two daytime severity items (at rest: r=.45, when active: r=.41). In a second cabergoline trial (n=40, mean age 56 years, 72% females) using polysomnography, correlation of baseline PLMAI and the RLS-6 scales were between r=-0.11 (daytime sleepiness) and r= +.23 (severity at bedtime) compared to the correlation of the IRLS total score and the PLMAI of r= +.008. When changes between baseline and endpoint after five weeks of treatment with either 2 mg cabergoline or placebo where analyzed, significant differences in favor of cabergoline could be demonstrated for all scales with the exception of severity at bedtime and tiredness during the day. Maximum effect size (95% CI) was observed for "severity during the night" [-6.01; -1.80].
Conclusion: The RLS-6 scales are qualified with respect to psychometric properties for the evaluation of specific (severity of symptoms at different periods of a 24 hour day) and unspecific (quality of sleep, daytime tiredness / sleepiness) symptoms of RLS. They are sensitive for treatment differences between active therapy and placebo. Therefore, the scales are suited for efficacy assessment in drug trials in RLS research.

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Prevalence of Restless Legs Syndrome among the Elderly in Japan

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Introduction: Prevalence of restless legs syndrome (RLS) has been studied in North America and Europe, however, there have been only a few epidemiological studies conducted to reveal the prevalence of RLS in the Japanese population. In addition, most of the previous studies in Japan were not based on standard RLS definition criteria. The aim of this study was to investigate the prevalence of RLS among Japanese elderly population using standard diagnostic criteria.
Methods: A countryside town with a population of about 6000 was chosen for the study. There were 1510 people with the age of 65 years and more, and a sleep questionnaire was given to 1440 community-dwellers. The questionnaire contained five questions about RLS symptoms; presence of urge to move associated with leg disconfort or paresthesia, worsening of symptoms by rest, relief of symptoms by movement, nocturnal worsening, and difficulty initiating sleep due to the symptoms. RLS was suspected when subjects answered "yes" to the first four questions. The prevalence was estimated after face-to-face interview on home visit by neurologists-sleep specialists for those who were suspected of having RLS from the questionnaire survey in order to rule out false positive cases based on NIH consensus conference diagnostic criteria (2003). We also examined the clinical characteristics and the extent and severity of sleep disturbance due to RLS symptoms in the final population that was diagnosed as having RLS.
Results: 1360 subjects (568 men, 792 women) responded to the questionnaire (response rate 94.4%). Of them, 103 subjects (7.6%; 51 men, 52 women) were suspected of having RLS from the questionnaire survey. Face-to-face interview was performed on 88 subjects (42 men, 46 women) and 19 of them fulfilled the diagnostic criteria of RLS, thus the overall prevalence of RLS was 1.4%. Mean duration of the RLS symptoms was 5.6±4.9 and mean frequency of the symptoms was 3.3±2.8/week. Six patients with RLS had lumber or cervical problems. 11 of the RLS patients complained of mild disturbance of initiating sleep, but none of them complained of severe sleep disturbance due to RLS.
Conclusion: Prevalence of RLS in the elderly population in Japan is lower than the previous reports in western countries. The severity of RLS in this population is mild and their motor/sensory symptoms do not cause at least severe insomnia.

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Restless Legs Syndrome and Periodic Limb Movements during Sleep among Hemodialysis Patients

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Introduction: Restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) are known to occur frequently in patients receiving hemodialysis (HD). However, there has been few systematic

analysis of RLS/PLMS in HD with polysomnographic (PSG) investigation with large number of subjects. The aim of the study was to correlate the presence of RLS/PLMS with subjective sleep disturbance, and to identify background factors relevant to the occurrence of RLS/PLMS.
Methods: 143 patients (82 males, 61 females, mean 62.4±10.1 years) who underwent PSG were included in the study. Detailed clinical interview and neurological examination were undertaken on all patients. Diagnosis of RLS was made according to the diagnostic criteria by the International Restless Legs Syndrome Study Group (IRLSSG). PLMS were measured with the PSG. Subjective sleepiness and quality of sleep was assessed by using Epworth Sleepiness Scale (ESS) and Pittsburg Sleep Questionnaire Inventory (PSQI).
Results: Diagnosis of RLS was made on 41 patients (28.7%, 19 males and 22 females). In 33 patients, RLS symptom appeared after the introduction of HD, and its duration ranged from 0.1 to 18 years (mean 5.1±5.0 years). PSG finding revealed that mean PLM index (PLMI) was 43.3±47.5/h and mean PLM arousal index (PLMAI) was 15.2±21.1/h. PLMI of more than 5/hour was recognized in 96 patients (67.1%). Patients were divided into three categories: 47 PLMS(-) patients, 32 PLMS(+)/RLS(-) patients and 54 PLMS(+)/RLS(+) patients. Although ESS as well as PSG parameters including PLMI, PLMAI and apnea hypopnea index did not differ between the three groups, mean PSQI score in PLMS(+)/RLS(+) group was 9.3±4.1 which was significantly higher than that in both RLS(+)/PLMS(-) group (6.4±4.2) and PLMS(-) group (5.8±4.3). Background factors including coexistence of diabetes mellitus and HD parameters did not show any statistical difference between the three groups except that the percentage of the patients with sensory disturbance of the lower extremities was significantly higher in PLMS(+)/RLS(+) group than in the other two groups.
Conclusion: This report is the first to describe the prevalence of polysomnographically determined PLMS in HD patients, and the result indicated that the PLMS was highly prevalent among the subjects. However, the results of ESS indicated that PLMS would not cause excessive daytime sleepiness, a typical symptom of periodic limb movement disorder. Our study indicated that the insomnia assessed by the PSQI was correlated with the presence of PLMS/RLS in patients receiving HD. Although we could not identify the causal factor for the high prevalence of PLMS/RLS among background variables, it was noteworthy that sensory disturbance was most frequently recognized in PLMS(+)/RLS(+) group. This finding might indicate that peripheral neuropathy is involved in the pathogenesis of PLMS/RLS in HD patients.

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Polysomnographic Studies in de novo Parkinson's Disease
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Introduction: Excessive daytime sleepiness (EDS) in Parkinson's disease (PD) is due to either treatment-related factors or the disease itself. Most studies on sleep disorders and EDS in PD have been conducted on patients being treated with dopaminergic drugs. The study of this disturbing phenomenon in de noveo parkinsonian patients may contribute to a better understanding of its pathophysiology. We compared polysomnographic studies in PD who had never been treated before with dopaminergic drugs (de novo) with those of healthy controls.
Methods: We conducted a case control study in which we compared 7 de novo PD (4 men, mean age 63.2) and 10 healthy control (6 men, mean age 62.8) subjects, all of whom were matched for age and gender. Severity of PD was rated by means of Hoehn and Yahr (H&Y) staging. The Mini Mental Stagte Examination (MMSE) was used as a screening procedure for assessment of dementia, and the Beck Depression Inventory (BDI) was used for evaluation of depression. EDS was measured by means of the Epworth Sleepiness Scale (ESS).
Results: PD patients had a reduced total sleep time (313.5 minutes) compared to healthy controls (365.4 minutes). Furthermore, there was a reduced sleep efficiency (74.5 vs 84.5), increased WASO (wakefulness after sleep onset)(55.6 vs 37.6 minutes, P=0.034), and higher ESS scores than controls (13.2 vs 9.3, P=0.03). There were no differences in the periodic leg movements index, MMSE and BDI. PD patients demonstrated an increased number of apnea-hypopnea index (AHI) as compared to controls (17.4 vs 2.1, P=0.026), which might explains the EDS. 5 PD patients were included in obstructive sleep apnea syndrome and 2 PD patients were included in upper airway resistance syndrome (UARS). There was no relation between severity of PD and AHI. Two PD patients demonstrated increased muscle tone during NREM and REM sleep without any violent movements.
Conclusion: Conclusions: This study suggests that parkinsonian patients (PD) who had never been treated before with dopaminergic drugs had a significant incidence of sleep breathing disorder compared to controls. Excessive day time sleepiness in PD may be due to underlying obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS).

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Efficacy and Tolerance of Transdermal Lisuride TTS patches in Patients with Severe Restless-Legs- Syndrome: a Proof-of-Concept Study
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Introduction: Lisuride is an effective dopaminergic treatment for parkinsonian patients. Besides the oral administration, recently a new transdermal form has been developed to achieve continuous, reliable and individually controllable dopaminergic stimulation. It is expected that treatment complications of oral therapies for the Restless-Legs-Syndrome (RLS) like rebound and augmentation effects can be avoided. In this proof-of-concept study, first administration of lisuride patches in RLS-patients was investigated.
Methods: Patients with severe idiopathic RLS (International RLS Study Group Rating Scale total score > 20 (range 0 to 40, 40 = very severe symptoms), RLS-6 scale "severity during the day when at rest" ≥ 4 (range 0 to 10, 10 = very severe symptoms)) were treated initially in an open label design with one TTS patch containing 3 mg lisuride. Patches were changed every 48 hours. In the event of insufficient efficacy after 1 week, dose was increased to two patches. Patients who responded to treatment after two weeks (defined as any positive rating in the CGI item "therapeutic efficacy") entered a double-blind, one-week study period wherein patients were randomized either to continue the current lisuride treatment, or to placebo. Efficacy was assessed by severity scales (IRLS, RLS-6 scales, CGI, Epworth Sleepiness Scale ESS, sleep questionnaire, sleep diary) as well as by actimetry (MOVOPORT, Rimkus, Munich, Germany). Systemic and local tolerability of the lisuride patches was determined by adverse event recording including laboratory and vital signs measures.
Results: All but one of ten patients (58 ± 4 years, 60% females) improved remarkably under open label treatment with lisuride patch therapy; IRLS total score: baseline (BL): 32.4 ± 5.9, change (d): -22.1 ± 11.8; RLS-6 "severity during the day": BL: 6.7 ± 2.4, d: -4.9 ± 2.6, actimetry / PLM/h: BL: 56.9 ± 41.0, d: -54.4 ± 28.4, all $p<.05$, signed rank test). Dose had to be increased in seven patients. Of nine patients who entered the double-blind study period, five patients were treated with lisuride and four patients with placebo. In all of the placebo patients, severity of RLS worsened at the end of the double-blind period compared to the status at week 2 (IRLS: +11.5 ± 10.9; RLS-6: +1.3 ±

1.5; PLM/h: +20.3 ± 26.5). In all lisuride treated patients, favorable treatment effects of the open label period could be further improved, compared to week 2 (IRLS: -1.4 ± 5.9; RLS-6: -0.4 ± 0.5; PLM/h: -6.0 ± 6.6). Similar improvements during open-label treatment and lisuride-placebo differences were observed in the further efficacy measures. Adverse events were observed in five patients; most frequently mild to moderate nausea (n=3) and vomiting (n=1) and skin reactions (n=2) were reported.
Conclusion: From the data of this proof-of-concept study in severely disabled RLS patients, further evaluation of lisuride TTS patches in RLS is recommended. Upcoming studies should address the dose-response relationship including higher and lower doses of lisuride, rebound and augmentation phenomena, and long-term treatment outcome with respect to efficacy and safety.

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Neurophysiologic Characteristics of Restless Legs Syndrome
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Introduction: Restless Legs Syndrome (RLS) is characterized by limb dysesthesias causing a distressing urge to move, worse at rest and in the evening, and relieved by activity. Although its etiology is unknown, the prominent sensory phenomena suggest that abnormal afferent input may play a role. Peripheral nerve disease has been reported in 1/3 of patients, mainly Large Fiber Neuropathy (LFN) based on EMG studies. Small Fiber Neuropathy (SFN) has been reported in about 20% of RLS patients, based on skin biopsy. Large comprehensive electrophysiologic studies of large and small fiber nerve function in RLS have not been reported. Our objective is to describe the neurophysiologic characteristics of RLS. We postulate that SFN, which often presents with dysesthesias in the feet, may underlie some cases of RLS, and may be important in its pathogenesis.
Methods: In this cross-sectional study, adult patients meeting the International RLS Study Group diagnostic criteria for RLS were recruited from Neurology Clinics at a tertiary hospital. Large Fiber studies were performed: EMG and quantitative sensory testing (QST) for vibration detection thresholds (VDT). Small Fiber studies included QST for cooling detection thresholds (CDT), quantitative sudomotor axon reflex testing (QSART) which assesses postganglionic sympathetic sudomotor function, and testing for Heart Rate Responses to Deep Breathing (HRDB) and the Valsalva Ratio (VR), which both assess cardiovascular autonomic function.
Results: 54 patients were studied (37 female, 17 male) with a mean age of 52 (range 25-81) years. 46% had a positive family history. 48% had pain in the limbs. EMG: Of 23 patients with abnormalities, only 6 (11%) had unequivocal LFN (3 sensory neuronopathy, 2 sensorimotor polyneuropathy, 1 sciatic neuropathy). 1 patient with sensory neuronopathy had HIV infection. The sciatic neuropathy may have been iatrogenic, related to knee surgery. No clear underlying etiology was detected in the rest. The remainder had nonspecific changes including age-related absent sensory potentials and chronic neurogenic changes in the feet probably related to repeated trauma. QST: 43% had abnormal VDT, 48% had abnormal CDT. QSART: Sweat volume production measured at 4 sites (forearm, proximal leg, distal leg, foot) was unequivocally abnormal in 34%, defined as diminished sweat production at the foot alone, or at 2 or more proximal sites. Overall 43% had LFN based on EMG and VDT. 70% showed abnormalities in at least one of the tests of small fiber function. Further evaluation of this group for an underlying etiology revealed hypothroidism (1), vitamin B12 deficiency (1), monoclonal gammopathy (1), a high random glucose (1) and ANA positivity (1). Oral glucose tolerance testing was not performed.
Conclusion: Our findings support the hypothesis that SFN may be important in the pathogenesis of RLS. The higher prevalence (70% vs 22%) of SFN based on electrophysiologic studies compared to morphometric examination may reflect the fact that small fiber studies detect early, subclinical abnormalities in different pathways (pain, sudomotor, autonomic) in both the upper and lower extremities. Abnormalities on skin biopsy, sampling only the distal leg may represent more advanced disease with loss of small fiber density. The presence of pain did not differentiate between those with or without SFN. The combined small fiber test battery (QST, QSART, HRDB, VR) increases sensitivity in the electrodiagnosis of SFN. The significance of these subclinical findings needs further study. Electrophysiologic small fiber studies should be considered in the evaluation of RLS, with the highest diagnostic yield from QST and QSART combined. Early recognition and specific therapy for RLS patients who have SFN with treatable etiologies (eg. impaired glucose tolerance, vitamin deficiencies, vasculitis) may improve outcomes in this common and disabling disease, symptoms may also respond to drugs used for neuropathic pain, such as the anticonvulsants.

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A Novel 2-step Diagnostic Approach for RLS Disease Classification
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Introduction: The diagnosis of RLS relies upon expert clinical opinion that hampers epidemiologic and genetic linkage studies. The latter would benefit from a rapid, inexpensive, objective measure for phenotyping a large number of patients. Here we demonstrate the utility of a diagnostic algorithm based upon ambulatory monitoring of periodic leg movements in sleep (PLMs) over 5 nights employing PAM-RL detectors (IM Systems, Baltimore, MA).
Methods: Validation of the ambulatory PAM-RL monitor was performed by comparison with "gold-standard" clinical polysomnography. Eight individual monitors were used in 41 subjects. Bilateral surface tibialis EMG recordings, analyzed separately for each leg, were used to generate a PLMs Index (PLMi) according to conventional criteria and blind to the PAM-RL results. In order to emulate the actual usage of the ambulatory monitors likely to occur "in the field", we determined start and stop times solely by reference to the up-down body position marker. RLS was then identified empirically by: 1) recruitment of potential subjects based upon IRLSSG consensus criteria; 2) ambulatory monitoring of PLMs over 5 nights; and 3) validation of disease categorization of a subset of subjects employing the present "gold standard" for diagnosis - viz., expert clinical opinion. Five hundred and fourteen Icelanders responded to an advertisement in print media as experiencing an urge to move along with an unusual sensation when inactive, as well as endorsing symptoms that: 1) were alleviated by movement; and/or 2) peaked in the evening or at night.
Results: Of the 8 monitors tested, 7 provided valid data. Examination of 70 pairs of PLMi simultaneously recorded with the PAM-RL and PSG revealed an overall Spearman correlation coefficient (rho = 0.74) suggesting moderately strong correspondence between the two metrics of PLMs. Disease status determined from semiquantitative analysis of PLM pattern and PLMi in subset of 124 subjects was determined to be positive (56%), probably positive (14%); probably negative (12%); and negative (17%). Post-hoc analysis of half of this sample subset revealed

that PLMi differentiated the 4 diagnostic categories based upon medians of the mean PLMi with one-way Analysis of Variance ($p<0.0001$): positive (24.8+ 21.1), probably positive (7.4 + 2.9), probably negative (2.73 + 2.1), and negative (2.0 + 1.2). Disease classification was then validated against the present 'gold standard', i.e. clinical impression blind to the questionnaire and PLMs results. Classification derived from questionnaire in combination with PLMi data demonstrated a positive predictive value of 98% (69 of 70) and negative predictive value of 58% in this enriched sample.
Conclusion: This 2-step approach demonstrated excellent diagnostic accuracy. False positives (97% specificity) are an unlikely source of error that might confound widespread application of this methodology to the larger populations necessary for genetic and epidemiologic studies. Rather, false negatives (75% sensitivity), represent a confound that might negatively impact the power of this approach. False negatives likely reflect the extreme variability in disease expression and/or its partial treatment that will be minimized by focusing phenotyping efforts on familial clusters.

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REM Behavior Disorder in Parkinson Disease: Clinical Interview And Polysomnographic Assessment

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Introduction: REM behavior disorder (RBD) is a sleep disorder characterized by an intensive motor pattern. In particular, the augmentation of muscle tone and the presence of excessive chin or limb EMG twitching during REM sleep reflect a critical dysfunction of movement control. Therefore, it is not surprising that RBD may be the first manifestation of extrapyramidal diseases and may be commonly found in patients with synucleinopathies. This study aims at investigating the presence of RBD motor features in a group of patients with Parkinson disease (PD).
Methods: Fifty patients with a diagnosis of Parkinson disease according to Gelb criteria and with different degree of severity were investigated. A semi-structured interview (questionnaire) based on the ICSD minimal clinical criteria evaluated the presence and frequency of RBD. According to the questionnaire results each patient could be classified as positive (positive answer to all the ICSD minimal criteria) or negative (negative answer to all the ICSD minimal criteria). Six positive patients were matched with 6 negative patients on the basis of balanced age, gender and clinical features including the age of onset and duration of PD. All patients were chronically treated with L-dopa and/or DA-agonists. The 12 patients (8 men and 4 women) underwent a polysomnographic (PSG) investigation. The PSG findings for RBD were at least one of the following during REM sleep: excessive augmentation of the chin EMG tone; excessive chin or limb EMG twitching, or both, regardless of chin EMG tone.
Results: No clear dream-enacting episodes similar to the ones described in the questionnaire occurred during the recording nights. All the positive patients showed both excessive augmentation of the chin EMG tone and excessive chin or limb EMG twitching. All the negative patients showed excessive chin or limb EMG twitching and in all cases but one REM sleep was associated with a normal muscle atonia.
Conclusion: The diagnosis of RBD is currently based on both clinical and PSG criteria. The main feature is the violent injurious behavior closely related to a dreaming experience. This aspect was consistently collected by the questionnaire and allowed classification of the positive cases. However, the lack of a clinical history for this nocturnal REM parasomnia may be associated with some motor abnormality in the PSG. Indeed, all the negative cases showed an excessive twitching, a PSG feature that has been indicated as a subclinical form of RBD in the absence of a clear behavioral manifestation. However, excessive twitching can be found in other sleep-related movement disorders without the typical clinical framework of RBD. Alternative hypotheses stress the pivotal role of REM without atonia in the definition of subclinical RBD. These issues are currently debated and require further investigation. A discussion on the normative data, nosographic boundaries and the role of PD medication is also advisable.

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Clinical Features of Restless Legs Syndrome in Iceland

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Introduction: RLS has never been systematically defined in Iceland. The Basic Nordic Sleep Questionnaire that was developed in Iceland and Finland for population based studies, in fact, lacks questions that probe for RLS. Here we provide the first comprehensive description of RLS in the Icelandic population as a prerequisite to a recently initiated genetic linkage analysis of RLS
Methods: We identified RLS subjects from a group of 514 answering an advertisement as experiencing an urge to move the legs together with an unpleasant sensation when inactive, as well as endorsed one of the following: 1) symptom alleviation with movement; and/or 2) symptom peak in the evening or at night. All patients answered an additional 80-item questionnaire. We established positive disease status with a novel, validated two-step algorithm which relied upon ambulatory monitoring of PLMs over 5 nights (98% positive predictive value; see accompanying abstract Rye et al.).
Results: A total of 196 subjects were deemed "positive" for RLS (median of the mean PLMi>20/hour). The mean age was 53.5 (range, 18-83) years and 63.3% were female. The most common terms for RLS were fótapirringur (literally translated - foot annoyings/irritation) and fótaóeird (i.e., foot without rest). Onset of RLS occurred before the age 30 years in 58.9% of individuals. Insomnia due to RLS was reported by 70%. Of these, sleep disturbance was categorized as severe by 32.9%. Involuntary leg jerks were appreciated both while waiting to fall asleep (66.4%) and during sleep (33.3%). A considerable number of subjects reported symptoms of RLS in the upper extremities (26.8%), and adverse effects of RLS on mood (84%) and ability to perform activities of daily living (ADLs) (80%) were endorsed. There was a suggestion of seasonal worsening in the winter months. Factors exacerbating RLS were fatigue (83.5%), pregnancy (39.2%) and alcohol (13.6%). Clinical conditions associated with RLS were hypertension (31.9%), iron deficiency (29.3%), anemia (23.5%), varicose veins (19.6%) and renal disease (4.6%). Early-onset cases (beginning < 30 y.o) were more likely to report having close relatives with RLS (70% vs. 25%; $p<0.001$), symptoms in the upper extremities (34% vs. 18%; $p<0.01$), iron deficiency (34% vs. 19%; $p<0.01$) and greater likelihood of symptom exacerbation during pregnancy ($p<0.001$). Women made up the vast majority of those with early life symptom onset (74%, $p<0.05$).
Conclusion: We have systematically defined RLS and found its clinical characteristics in the Icelandic population to emulate that described in other nations. The features of RLS in Iceland suggest a severity greater than that encountered elsewhere. This is reflected in greater incidence of symptoms in the upper limbs, earlier age of onset, and adverse effects upon sleep, mood and ADLs. Nonetheless, less than one-in-five subjects had reported symptoms to their doctor - the vast majority, therefore, were not diagnosed/treated. Striking differences in clinical characteris-

tics exist between early and late-onset RLS. A significant genetic component in the causation of early-onset RLS is suggested by the high incidence of affected first-degree relatives.

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To Be Excluded Or Not: How Periodic Leg Movement Index Influences Polysomnographic Sleep In Middle-Aged Subjects Without Sleep Complaints?

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Introduction: Typically, studies that aim to evaluate the mechanisms underling age-related modifications to the sleep-wake cycle exclude an important proportion of subjects because of strict research criteria to attenuate the confound variables associated with aging. Our knowledge on aging and sleep is then almost entirely based on supra-normal aging. Since periodic leg movement index (PLMS) increases with age, it becomes one of the most important exclusion criteria in research on middle-aged subjects when strict criteria are used (PLMS index <5). Some reports have strongly suggested that PLMS index is not related to subjective sleep complaints in older subjects. However, it is unknown if PLMS index is related to polysomnographic sleep architecture in middle-aged subjects without sleep complaints.
Methods: The sleep of 70 healthy middle-aged subjects (40-60y, mean=51.3, SD=5.0) was evaluated. Subjects volunteered to participate in different studies on sleep and circadian rhythms in our laboratory. Participants were in good health according to medical history and they reported no sleep complaints. All subjects were recorded for one screening night in the chronobiology laboratory. Polysomnography (PSG) included four EEG derivations (C3/C4, O1/O2, linked ears), right and left electrooculogram (EOG) and chin electromyogram (EMG). Surface EMG of both right and left anterior tibialis muscles were recorded to quantify PLMS. Subjects were divided in two groups according to their PLMS index severity: 1) 43 subjects (28 women, 15 men, 51.5 y, SD:4.9) were in the low PLMS index group (index <5) and 2) 22 subjects (9 women, 13 men, 52.3 y, SD:4.4) were in the high PLMS index group (index >10). Two-factor Anovas (Gender, PLMS Index severity group) were performed to evaluate differences on polysomnographic sleep parameters.
Results: In this sample, 76% of middle-aged women and 53% of middle-aged men showed a PLMS index of less than 5 while 24% of middle-aged women and 46% of middle-aged men showed a PLMS index higher than 10. Mean PLMS index was 1.0 (SD=1.2) for the low PLMS index group and 26.8 (SD=19.7) for the high PLMS index group. No significant effect of PLMS index severity group was found for sleep latency, sleep duration, minutes and % of stages 1,2,3,4 and REM, number of microarousals and sleep efficiency. Indeed sleep architecture was very similar between the two groups. For example, the low PLMS group showed a sleep efficiency of 87% (SD=11) while the high PLMS group showed a sleep efficiency of 85% (SD=11). No significant effect of gender or interaction between PLMS index severity group and gender were found.
Conclusion: PLMS index did not affect sleep polysomnographic parameters in healthy middle-aged subjects without sleep complaints. These results challenge the notion that very strict exclusion criteria for PLMS index should be used in research on age-related modifications of sleep-wake cycle mechanisms.

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Age-Related Changes In Leg Movements During Sleep And Wakefulness In Normal Subjects

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Introduction: Several studies have demonstrated a positive correlation between periodic limb movements during sleep (PLMS) and age in normal populations. However, little is known about movements during wakefulness in control groups. The aim of this study was to measure periodic leg movements during nocturnal periods of wakefulness (PLMW) and the spontaneous motor activity during nocturnal wakefulness in a control population in relationship with age.
Methods: Forty seven control subjects who have participated in different research projects were selected for this study. They were aged between five and 76 years old (mean age: 36.2 ± 23.1 years, 23 females, 24 males). All subjects were studied in the sleep laboratory between 1999 and 2003. None of the patients had any associated medical or sleep disorder. They were not taking any medication known to influence sleep or motor activity. Subjects with a respiratory event index of five or more per hour of sleep were excluded. As we were also evaluating movements index during nocturnal wakefulness, sleep efficiency was controlled. Subjects with a sleep efficiency lower than 80% were excluded. As we also wanted to verify movements' evolution with age, we did not exclude subjects on PLMS or PLMW criteria. PLMS were calculated following Coleman criteria. PLMW were calculated following modified Coleman criteria, allowing for movement duration up to 10 seconds, whereas the spontaneous motor activity index during wakefulness included all movements between 0.5 and 10 seconds, without any criteria for periodicity or minimal number of movements. Pearson Product-Moment correlation coefficients were calculated between age on one hand and PLMS index, PLMW index and spontaneous motor activity index during wakefulness on the other hand.
Results: A significant positive correlation ($r = 0.54$) was found between age and PLMS index ($p = 0.0001$) which is consistent with previous studies. A significant negative correlation ($r = - 0.30$) was observed between age and PLMW index ($p = 0.04$). For the spontaneous activity index, a significant negative correlation ($r = - 0.29$) was also found with age ($p = 0.05$).
Conclusion: Previous studies did not find consistent correlation between PLMS index and PLMW index. The present study, shows that PLMW have in fact an inverse relationship with age. These results suggest that in a normal population, different mechanisms are probably involved in generating movements during sleep and during wakefulness. Further analysis will evaluate characteristics and the periodicity of leg movements occurring during wakefulness in normal subjects of different age groups. PLMS and PLMW are often used as supportive criteria for RLS. Results of the present study suggest that PLMW index would be a better supportive criterion for older RLS patients whereas PLMS index would be a better supportive criterion for younger RLS patients.

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The Efficacy of Pramipexole in the Treatment of REM Behavior Disorder

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Introduction: Rapid eye movement (REM sleep) behavior disorder (RBD) is characterized by a prominent behavioral and phasic electromyographic (EMG) activation during REM sleep. It is found primarily in older males, often predating the onset of neurodegenerative diseases by approximately a decade or more. RBD also has a known association with narcolepsy. Acting out during REM sleep can have serious safety implications from the violent dream enacting behaviors. Although current therapy with clonazepam is effective, treatment alternatives may be desired in subjects sensitive to its sedating effects such as in some elderly patients or narcoleptics. The common association of RBD with periodic limb movement disorder (PLMD) or Parkinsonism suggests a potential role of decreased dopaminergic neurotransmission in the expression of RBD. We performed a prospective case series with pramipexole, a D2-D3 agonist, for the treatment of RBD.
Methods: All patients presenting with RBD over a 14-month period were placed on pramipexole and followed over 2-6 month intervals for an average follow-up of 8.8 months. Subjects underwent polysomnography prior to treatment initiation for evaluation of concomitant sleep disorders and confirmation of phasic EMG and/or behavioral activation during REM sleep. Titration began at 0.25 mg for a maximum total evening dose of 1.0 mg in either a single or divided dose regimen (with the first dose given in the early evening).
Results: 11 consecutive patients presenting with RBD were placed on pramipexole. The mean age was 72.9±1.9 years old (range 60-80) and predominantly male (10/11). Concomitant sleep disorders were common in this population with 5 demonstrating mild obstructive sleep apnea (A+HI>10), 5 with restless legs syndrome, 6 with PLMD (PLMDI>5.0), and 2 with previously undiagnosed narcolepsy. Two patients had mild Parkinsonism, and a third had recent cognitive impairment. RBD symptoms essentially resolved in all patients with a mean total evening dose of 0.6±0.1 mg (range 0.25-1.0 mg), all but one patient requiring at least 0.5 mg. Although RBD symptoms essentially resolved in two patients on pramipexole, rare talking or moaning in sleep persisted. Only one patient had previously been on clonazepam and found RBD to be equally well controlled when switched to pramipexole. Adverse events were uncommon and generally limited to nausea, except one patient who had hallucinations resulting in the only medication withdrawal.
Conclusion: This is largest prospective study demonstrating the effectiveness of pramipexole in the treatment of RBD. Titration of pramipexole to an evening dose of 0.5-1.0 mg essentially resolved RBD symptoms in all patients of this prospective sample. Adverse events were limited to nausea and one patient with hallucinations. Concomitant restless legs syndrome (5/11 patients) and symptoms of Parkinsomism (2/11 patients) also resolved or improved with pramipexole. Given the utility of this dopaminergic agonist in simultaneously treating other common dopamine-responsive disorders in this patient population and the potential unwanted sedating effects of clonazepam, we propose that dopaminergic agonists should be considered as a first-line therapy for RBD.

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Age Of Onset And Family History Of RLS

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Introduction: Although RLS was considered for a long time as a condition of middle-aged people. Recent studies have shown that it actually starts early in life in a significant number of patients. On the other hand, a large proportion of RLS patients have positive history, and familial aggregation was found in more than 50% of RLS patients. It has been recently showed that early onset was associated with a higher likelihood of a positive family history of RLS. The aim of the present study was to confirm this hypothesis in a large independent sample and to further characterize, both clinically and polygraphically, patients with positive and negative family history.
Methods: Two hundred and twenty seven (227) patients who fulfilled all 4 criteria for RLS entered the study. None of the patients had any condition known to be associated with RLS or took any medication likely to influence sleep or motor activity. All were recorded for at least 1 night in the sleep laboratory. In addition, they completed a questionnaire about the age of onset of their RLS symptoms and the presence or absence of a family history of RLS.
Results: One hundred and forty three patients (63%) presented a positive family history i.e. they had at least one first-degree relative affected with RLS. Comparison between those with and without a family history revealed a significant difference with regard to age of onset (28.9 vs 34.4; p=0.016). In two thirds (65%) of family cases, RLS occurred at age 30 or younger compared to 47% of non-familial cases. However, there were no between-group differences for RLS severity, PLMS index and PLMW index. In patients with a positive family history, the age onset showed a bimodal distribution with one major peak between 15 and 20 years of age and a smaller peak in the early forties. Patients without a family history of RLS showed a more even distribution across age groups.
Conclusion: These results confirmed that in familial cases RLS starts earlier in life. However, it is sometimes difficult to define accurately the onset of the disease retrospectively. Moreover, the identification of the exact time of onset depends on the delay between the date of the occurrence of the first symptoms and the date of the first interview. As in RLS, a bimodal distribution of age of onset was found recently in narcolepsy. As in narcolepsy, the results obtained in RLS patients may indicate that the age of onset of RLS is genetically determined. Further research will be needed to further explore this hypothesis.

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Relationship Of The Restless Legs Syndrome Rating Scale Scores To Objective And Subjective Measures Of Sleep

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Introduction: Restless legs syndrome is a neurological disorder that often profoundly disturbs sleep. Sleep disturbance is one of the common complaint of patients and mostly the reason the patient seeks medical help. The RLS severity rating scale (IRLS) designed by the International

RLS Study Group is a ten-question scale to measure disease severity for clinical and research assessment. The IRLS was found to have high levels of consistency, reliability and validity. It is not known, however, to which extent the scale correlates with measures of sleep. In the present retrospective study, we evaluated the relationship of the IRLS score and of polysomnographic and subjective measures of sleep.
Methods: Polysomnographic data and rating scales of 35 patients with RLS (according to the IRLSSG diagnostic criteria) were evaluated (24 females and 11 males, age 57 +- 11 yrs). Patients were free of any dopaminergic or other psychotropic medication or substances influencing sleep. Polysomnographic recordings with monitoring of periodic leg movements in sleep (PLMS) were performed for two consecutive nights. The patients sleep perception was assessed by the Pittsburgh Sleep Quality Index (PSQI).
Results: The mean IRLS score was 25.1 +- 6.3 (range 14 - 37) indicating a severe affection of the investigated patients by the disorder. The polysomnographically evaluated sleep efficiency was 76.5 +- 13.2 %, the PLMS index (number of PLMS per hour of sleep) amounted 31.3 +- 31.4 /h and the PLMS arousal index (number of PLMS associated with arousal per hour of sleep) 13.0 +- 15.4 /h (for all parameter means of both investigated nights). The PSQI score revealed slightly to moderately reduced subjective sleep quality (11.0 +- 3.8, range 3 - 18). The IRLS sum score correlated with the sleep efficiency in the first night ($r = -0.388$, $p < 0.05$, Spearman-Rho) but not in the second night. Similarily, the score of question 4 (regarding the subjective severity of sleep disturbance) correlated with sleep efficiency only in the first night ($r = -0.460$, $p < 0.01$) but not in the second night. There was no relationship either of the IRLS sum score and of PLMS indices nor of the IRLS question 4 score and of PLMS indices. The PSQI score correlated with scores of the IRLS question 4 ($r = 0.422$, $p < 0.05$, $n = 28$).
Conclusion: The IRLS correlates with most of the assessed subjective and objective measures of sleep. The findings should be confirmed in a greater patient population.

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The Prevalence and Outcomes of Restless Legs Syndrome among Veterans

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Introduction: Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by unpleasant, abnormal feelings in the legs and occasionally arms which occur at rest or when initiating sleep, and in the evening or at night. Sufferers experience an uncontrollable urge to move to relieve these symptoms. RLS interferes with the ability to fall asleep or maintain sleep. Estimates of the prevalence of RLS in community populations ranges from 4% to 17%. A 29% prevalence has been reported in one VA outpatient sample. The goal of this research is to estimate the prevalence of RLS and insomnia among patients seen at VA primary care clinics. This research investigates an explanatory model in which RLS contributes to insomnia. Insomnia contributes to diminished mental health status and to increased health care utilization.
Methods: Study members were a representative sample of Veterans seen at Community Based Outpatient Clinics affiliated with the Louis B. Stokes Cleveland VA Medical Center in Ohio. A cross-sectional telephone survey was used to determine the prevalence of RLS and insomnia. Patients were classified as non-RLS cases, probable (3 criteria) or definite (4 criteria) cases. Health status was measured using the Mental and Physical Composite Scales (MCS and PCS) of the SF12. Utilization information was obtained from the patient and included: number of office visits, diagnostic procedures, hospitalizations, and surgical procedures. All tests of hypothesized relationships were adjusted for age, gender, Body Mass Index, and physical health status (PCS score).
Results: Preliminary results from 620 patients are reported. Forty-five percent of patients who were approached completed an interview. The sample included 544 men and 76 women, age range 25 to 89 years. Among men, the prevalence of probable RLS was 15.8%, definite RLS was 9.7%, moderate insomnia was 9.9% and severe insomnia was 3.3%. Among women, the prevalence of probable RLS was 19.7%, definite RLS was 14.5%, moderate insomnia was 26.3%, and severe insomnia was 7.9%. The insomnia score of an average patient increased 53% in the presence of 4 RLS symptoms ($p < .001$). In this VA sample, the mean MCS score was 50.3, similar to the US population mean. The mean PCS score was 39.9, one standard deviation below the US mean. The mean MCS score of persons with probable or definite RLS was significantly lower (41.0, $p<.01$), as was the mean MCS score of persons with moderate insomnia (40.6, $p <.0001$) and of persons with severe insomnia (34.7, $p<.0001$). As hypothesized, the association between RLS and the MCS disappeared when insomnia was included in the regression model. Analysis of utilization data obtained from patients found that neither insomnia nor RLS were associated with physicians visits. RLS but not insomnia was positively associated ($p = .04$) with diagnostic testing.
Conclusion: Preliminary analysis of approximately one third of the planned sample offered support for the hypothesized explanatory model. The final sample (n=1914) will allow precise estimates of RLS prevalence in age strata.

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Prevalence and Sleep Correlates of Periodic Limb Movements in Older Women: The SOF Study

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Introduction: Periodic limb movement disorder (PLM) has been associated with fragmented sleep, symptoms of insomnia and excessive daytime sleepiness in some, but not all studies. When defined by a PLM index (leg movements/sleep hour) (PLMI) > 5, prevalence in the elderly has been estimated to be between 25 and 58%, compared to about 5-6% for community-dwelling younger adults. The purpose of this study was to characterize the prevalence and severity of PLMs in a group of older women, and to assess whether increasing severity of PLMs are associated with objective evidence of poorer sleep quality.
Methods: The sample was drawn from the Study of Osteoporotic Fractures (SOF), an ongoing cohort study that enrolled 9704 Caucasian women between 1986 and 1988, and 662 African-American women between 1997 and 1998. In 2002, unattended overnight 12 channel in-home polysomnography (PSG) was performed in a subset of 436 women recruited from two of the six clinical centers at the eighth exam. Data were collected using the Compumedics Siesta Unit (Abbotsville, AU), with monitoring of two central EEGs, EOG, chin EMG, thoracic and abdominal respiratory effort, airflow (by a nasal-oral thermocouple and nasal pressure recording), finger pulse oximetry, electrocardiogram, body position, and bilateral leg movements with piezo sensors. Sleep

was staged using standard criteria by certified scorers blinded to data on the leg movement channels. Leg movements were scored according to AASM criteria (>4 consecutive 0.5 to 5 second movements, each separated by 5-90 seconds). Arousals were scored according to AASM criteria. Apneas and hypopneas were defined using Sleep Heart Health Study criteria, modified to include consideration of the nasal pressure signal. The apnea-hypopnea index (AHI) was defined as the mean number of respiratory events, each with a > 3% desaturation, per hour of sleep. Data were analyzed using Spearman rank correlations, ANOVAs or the Kruskal-Wallis test, and multiple linear regression.
Results: The sample had an average age of 82.8 ± 3.5 years [SD] (29% > 85 years), and 8.5% were African American. The mean arousal index (ArI) was 20.4±11.9 and sleep efficiency 74.3%±13.1. Median AHI was 11.3 and 38% had an AHI > 15. The median PLMI was 27.5 (0 to 185, range), with 73% showing a PLMI > 5. PLMIs of 5 to 15, 16-30, and > 30 were observed for 14%, 11% and 49% of participants, respectively. Elevated PLMIs were more frequent in the 127 women age >85 years compared to the remainder of participants 73 to 85 years (p=0.02). In addition, frequency of PLMIs increased with advancing age. Among women > 85 years, 82% had a PLMI > 5 and 60% had a PLMI > 30, as compared to 70% and 56% of younger women. PLMs were not associated with the AHI or underlying cardio-respiratory disease. An increasing PLMI was associated with an increasing arousal index(r=.15, p=.002) and lower percentage REM sleep (r=-.10, p=.03), but not with sleep efficiency or slow wave sleep. The relationship between PLMI and ArI (but not REM sleep) persisted following adjusting for age, ethnicity, and co-morbidity, with evidence for a threshold effect of increasing ArI at a PLMI > 30 (p=.03).
Conclusion: These data indicate that PLMs are even more common in the oldest old than previously appreciated, with evidence for a progressive increase in PLMs with advancing age. Among elderly women, PLMs are weakly associated with increased arousals, but not with evidence of increased perturbations of other indices of sleep quality. Further research is needed to better identify threshold levels of the PLMI, if any, that identify older subjects at increased risk for co-morbidity or functional limitations.

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External Validation Of The International Restless Legs Scale

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Introduction: The International RLS (IRLS) scale, the most commonly used clinical method of severity, has not been validated yet against objective parameters. The objective of this study was to test the external validity of the IRLS scale by assessing the correlation between IRLS scores, polysomnography (PSG), and suggested immobilization test (SIT).
Methods: The study included 30 untreated patients diagnosed with RLS according to the criteria of the IRLSSG. Diagnostic procedures included laboratory analysis, PSG, and a SIT performed between 2230 and 2330. Statistical analysis was performed by means of Spearman's correlations.
Results: 1. IRLS-scores correlated significantly with both Periodic Leg Movement of Sleep (PLMS)-index and PLMS-arousal index (r=0.4; p<0,01). No correlation was found between IRLS-scores and Periodic Leg Movements during Wakefulness (PLMW) recorded during PSG or with any other sleep variables. 2. IRLS scores correlated with PLMW on SIT (r=0.4; p<0,01). 3. Furthermore, PLMS during PSG were associated to PLMW during SIT (p<0,05). 4. No correlations were found between IRLS scores and ferritin, age, duration of illness or any other clinical variables.
Conclusion: This study represents the first external validation of the IRLS scale against objective parameters such as PLMS-index or SIT, and suggests that subjective and objective severity parameters of RLS are well related to one another. The finding is particularly relevant for the assessment of RLS severity and for the future design of clinical trials. Furthermore, the association between PLMS (during PSG) and SIT supports the view that both PLMS and PLMW might share a common mechanism.

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The Effects of Antidepressants on Leg Movements

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Introduction: It has been reported the serotonergic antidepressants induce periodic limb movements in sleep (PLMS), while bupropion reduces PLMS. Antidepressant (AD)-induced PLMS may be responsible in part for complaints of treatment-emergent or refractory insomnia in depression, and may limit the tolerability of some ADs. However, there are not enough systematic studies of the effects of various ADs on the development of PLMS. The results from this study may assist in the selection of AD, especially in patients with pronounced a sleep complaint.
Methods: Among patients referred for overnight diagnostic polysomnography, we selected consecutive 155 patients on AD (age 37.6±8.9, male 41.9%) and 68 controls without AD (age 39.3±8.0, male 38.2%). AD subjects consisted of 32 on citalopram, 25 on fluoxetine, 22 on paroxetine, 32 on sertraline, 26 on venlafaxine, and 19 on bupropion. We excluded patients with an RDI>30, with CPAP, taking 2 kinds of AD simultaneously, taking dopamine agonists, and with RLS, narcolepsy or medical illnesses such as uremia known to predispose to PLMS. Sleep scoring was performed based on standard criteria. Solitary leg movement (LM), periodic leg movement (PLM), alternating leg muscle activation (ALMA), and leg movement associated with apnea or other respiratory events (LMAp) were visually counted and their indexes were calculated (LMI, PLMI respectively). Leg movements with arousal (LMArI and PLMArI) were also computed. Statistical tests were performed with the student's t-test and chi-square test.
Results: There were no significant differences in sleep continuity, sleep structure, mean RDI, mean minimal SaO2, and mean ESS between AD and control groups. However, compared to controls, patients on ADs showed more solitary LMs in sleep (LMI 7.1±5.9 vs. 4.2±3.9. p<0.001; LMArI 2.5±1.9 vs. 1.6±1.6, p<0.001), more PLM during wake at night (PLMWI 0.7±0.6 vs. 0.5±0.3, p<0.05) and in sleep (PLMI 14.9±2.0 vs. 6.4±12.3, p<0.002; PLMArI 4.0±6.9 vs. 1.9±3.8, p<0.03). Thirty-four (21.9%) patients on AD had a PLMI of 25 or more, while 5 control (7.4%) had (p<0.001). PLM in patients on AD occurred most frequently in the second 1/3 of the sleep period (PLMI 22.6±39.5) as compared to the first 1/3 (PLMI 15.6±24.6, p=0.06) and the third 1/3 (PLMI 9.5±15.0, p<0.001). On the other hand, controls did not show significant difference in PLMI distribution throughout the sleep period. There was no significant difference in PLMI among the five serotonergic ADs. Patients taking bupropion had the lowest PLMI among ADs and did not show any significant difference compared to the PLMI of controls. Thirty-five patients (22.6%) showed ALMA at least more than one time, while 6 controls (8.8%) did. Thirty-seven percent (±24.1) of all respiratory events in patients on AD was followed by LMAp while this was present in 28.4% (±23.5) of controls (p<0.02).
Conclusion: This study suggests that serotonergic ADs (citalopram, fluoxetine, sertraline, and paroxetinevenlafaxine), but not the noradrenergic/dopaminergic agent (bupropion), induce a variety of leg movements

as well as PLMS. The clinical significance of these findings bears further exploration. References: 1. Atlas Task of the American Sleep Disorders Association. Recording and scoring leg movements. Sleep 1993;16:748-759 2. Dorsey CM et al. Fluoxetine induced sleep disturbance in depressed patients. Neuropsychopharmacology 1996;14:437-442 3. Nofzinger EA et al. Bupropion SR reduces periodic limb movements associated with arousal from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry 2000;61:858:862

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Long-Term Effect Of CPAP In The Treatment Of Nocturnal Stridor In Multiple System Atrophy (MSA)

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Introduction: In MSA, nocturnal stridor is common, results from vocal cord abductor dysfunction and is associated with sudden death during sleep and short survival. We previously showed that in MSA CPAP is a non-ivasive treatment which eliminates stridor (Iranzo et al., Lancet 2000;356:1329-1330). We now present our prospective analysis on the long-term efficacy and viability of CPAP in the treatment of laryngeal stridor in MSA.
Methods: Between April 1998 and December 2003, we studied 40 consecutive MSA subjects who underwent audiovisual-polysomnography (PSG) and laryngoscopy. Stridor was identified during PSG when a crowing harsh high-pitched sound occurred during breathing. Subjects with stridor underwent a second audiovisual PSG where CPAP was titrated to eliminate stridor. Survival rates were calculated using the Kaplan-Meier method from disease onset until the last follow-up or death. The mean follow-up from PSG to death or last follow-up was 21.1 +/- 15.2 months.
Results: Nocturnal stridor was detected in 14 patients (35%), 8 men and 6 women, with a mean age of 60.9 +/- 9.4 years. Laryngoscopy in 12 patients with stridor showed bilateral complete vocal cord abduction restriction in 3, unilateral complete vocal cord abduction restriction in 7, and bilateral partial complete vocal cord abduction restriction in two. When compared to subjects without stridor, patients with stridor had a significantly higher apnea-hypopnea index, lower oxyhemoglobin desaturations and higher number of patients with vocal cord paralysis. One subject refused to be treated with CPAP or any further treatment. In 13 patients, CPAP eliminated stridor and associated obstructive apneic events and oxyhemoglobin desaturations with a mean CPAP pressure of 7 +/- 2.2 (range, 4-11) cm H20. Two subjects did no tolerate CPAP at home. Eight of the 11 subjects who tolerated CPAP, underwent an audiovisual-PSG at optimal CPAP level after one month of therapy at home which confirmed the elimination of stridor, obstructive apneas and oxyhemoglobin desaturations. During follow-up, the 11 patients treated with CPAP reported using their machine every night, no side-effects, and subjective improvement in sleep quality and daytime vigilance. The mean CPAP treatment duration was 11.2 +/- 8 months. After several months of CPAP therapy, diurnal stridor worsened in two patients who also had stridor during wakefulness and emergency tracheostomy had to be performed. At the time of the study there were 42.4% patients alive in the non-stridor group (11 of 26), 36.4% in the CPAP-treated stridor group (4 of 11), and 0% in the untreated stridor group (0 of 3). None of the patients treated with CPAP died while sleeping. Median survival was not different between the non-stridor and CPAP-treated stridor groups (89 vs. 84 months, p=0.7). Median survival was significantly shorter in the untreated stridor group than in the non-stridor group (68 vs. 89 months, p=0.02). There was a trend for a shorter survival in the untreated stridor-group when compared with the CPAP-treated stridor group (68 vs 84 months, p=0.07).
Conclusion: In MSA patients with stridor CPAP is well tolerated, eliminates stridor, obstructive apneic events, oxyhemoglobin desaturations, and increases the median survival rate.

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Hypnic Headache:Polysomnographic Evidence of both REM and NREM Sleep-related Attacks

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Introduction: Hypnic Headache (HH) is a rare ,benign disorder, whose attacks occur exclusively during sleep. The physiopathogenesis and ultimate significance of HH are still unknown. The few polysomnographic findings available in the literature (in 7 out of the 71 published cases) indicate that HH attacks are closely associated with REM sleep and that Sleep Disordered Breathing (SDB) is not frequent in HH sufferers.
Methods: Ten patients (six women; four men; mean age 67.9, sd 6.6 years) fulfilling published diagnostic criteria for HH, were selected among the referrals to Headache Center of our Institute within a two-years period. Symptomatic forms of headache, including nocturnal arterial hypertension- related headache, were ruled out by means of Nuclear Magnetic Resonance of the brain and 24-hour, ambulatory monitoring of arterial pressure. The ten patients underwent sleep questionnaire and comprehensive, full-night polysomnography at the Sleep unit of the Institute.
Results: The polysomnographic features of sleep were typical both in NREM and in REM sleep.The mean Total Sleep Time(TST) was 366 min, sd 42.4 with a Sleep Efficiency Index of 79.5, sd 9.6. The mean Sleep Latency was 25 min. The mean REM latency was 129 min (range 78-178 min). Six HH attacks (a single attack in four patients, two attacks in one), were recorded during the PSG-monitored night. Four attacks arose directly from NREM sleep (two from stage 2 and two from stage 3) and two from REM sleep. In all the instances the attack was followed by an awakening. In no case epileptiform abnormalities were recorded before, during and after the headache attack. As far as breathing patterns are concerned, sporadic snoring and SDB were documented in four out of the ten patients studied. The SDB consisted of both NREM and REM related obstructive apneas and hypopneas (Mean Apnea/Hypopnea Index: 9.5, range 8-11; Mean HbSaO2 nadir:85.3 %, range 81-89%). In one "HH plus SDB" patient, HH attacks recorded did not show any close temporal relationship with breathing abnormalities.
Conclusion: Our data provide evidence that HH attacks occur in relation both to REM and NREM sleep suggesting that the relationship between HH and REM sleep is not exclusive and that the pathophysiology of HH with respect to hypnogenic mechanisms is heterogeneous. The PSG findings concerning breathing during sleep seem to belittle the role of SDB in the physiopathogenesis of HH. However the potential benefit of continuous positive airways pressure (CPAP) treatment could not be verified in our "HH plus SDB" patients. Thus in lack of these data no definite conclusion can be drawn on the possible influence of SDB in HH.

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Secondary Hypersomnia Cases Due To Hypocretin-Deficiency

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Introduction: CSF hypocretin-1 (orexin-A) level is dramatically decreased in most narcolepsy-cataplexy cases and rarely in other medical conditions. We report here several cases of secondary hypersomnia due to hypothalamic lesions, such as tumors, encephalitis, acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS).
Methods: CSF samples from 10 subjects with hypersomnia and bilateral hypothalamic lesions. Hypocretin-1 level in CSF was measured using radioimmunassay kits (Phoenix Pharmaceuticals, Belmont, CA). Clinical symptoms, brain MRI and CSF hypocretin-1 level were correlated.
Results: Case1: 16y, female, removal of a hypothalamic tumor, hypersomnia, hyperphagia and low hypocretin level (104pg/ml, normal range: 200-400pg/ml)(Arii2001) Case2: 45y, female, MS with hypersomnia and undetectable hypocretin level (less than 40pg/ml)(Kato2003) Case3: 21y, female, MS, hypersomnia, undetectable hypocretin level and sleep onset REM periods in MSLTs (5times in 5 naps). (Oka2004, J Neurol in press) Case4: 12y, female, ADEM, hypersomnia and low hypocretin level (102pg/ml)(Kubota2002) Case5: 40y, female, vasculitis, hypersomnia, diabetes insipidus, SIADH and low hypocretin level (75pg/ml)(Obara2004) Case6: 66y, female, hypothalamic tumor, hypersomnia, sleep onset REM period in the nocturnal PSG, cataplexy-like phenomena and low hypocretin level (61pg/ml)(Nokura2004, in this issue) Case7: 11m/F, hypersomnia due to ADEM, hypocretin less than 40pg/ml, (Yano2004, in this issue) Case8: 7y/F, hypersomnia due to ADEM with low hypocretin level (146pg/ml) (Yoshikawa2004, in this issue) Case9: 65/M, hypersomnia due to limbic encephalitis, hypocretin 92pg/ml (Yamato2004), Case10: 5/F, hypersomnia due to Wernicke encephalitis, hypocretin less than 40pg/ml (Kashiwagi2004, in this issue).
Conclusion: In most cases except case1, hypersomnia was reversible by treatments in parallel with the recovery of hypocretin levels. Therefore, hypersomnia was thought to be due to hypocretin-deficiency. Hypocretin neurons localize in the hypothalamic area which was previously discribed as 'waking center' by Von Economo in 1920s. Although there were many variations in accopaning symptoms, such as diabetes insipidus and hyperphagia, most above cases show both extended nocturnal sleep time and excessive daytime sleepiness consisting of prolonged (1-2 h) sleep episodes of NREM sleep. The features of nocturnal sleep and sleepiness are not same those of narcolepsy. While in the REM related symptoms, only two cases show sleep onset REM sleep periods and one of them showed cataplexy-like phenomena. The symptoms of above cases with hypocretin-deficiency are similar to idiopathic hypersomnia than those of narcolepsy-cataplexy. References: Arii J. Neurology. 2001;56(12):1775-6. Kato T. Intern Med. 2003;42(8):743-5. Kubota H. J Child Neurol. 2002;17(7):537-9.

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Subjective And Physiologic Measures Of Sleepiness In Head Injury Patients

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Introduction: Excessive daytime sleepiness (EDS) and fatigue are common complaints in head injury patients. The aim of this preliminary descriptive study was to compare the correlation between subjective and objective measures of daytime sleepiness in head injury patients and their relationship to mood.
Methods: Seven patients with a history of head injury (5 F, 2M; age range 33-68) participated in the study. All patients underwent overnight sleep polysomnography and were administered the Epworth Sleepiness Scale (ESS), Stanford Sleepiness Scale (SSS), Fatigue Severity Scale (FSS), the Profile of Mood States (POMS), and the Toronto Alexithymia Scale (TAS) (a measure of emotional connectedness).
Results: There was no association among the scores on the various self-report instruments of daytime sleepiness and fatigue. Five of the 7 subjects reported being excessively sleepy on the ESS, 3 out of 7 reported being sleepy on the SSS, 6 out of 7 reported excessive fatigue on the FSS scale and 2 out of 7 scored abnormally high on the fatigue subscale of the POMS. Five out of 7 patients scored outside the normal range on the TAS. Further, there was no relationship between subjective reports of sleepiness and physiologic measures. Only 2 of the 7 patients were found to have mild EDS on the Multiple Sleep Latency Test and Maintenance of Wakefulness test. Five patients had a sleep efficiencies above 80%. All patients had mild to moderate abnormalities in their sleep architecture and only one subject was found to have sleep apnea. The 2 patients with sleep efficiencies below 50% (neither had sleep apnea) both scored abnormally high on the POMS tension, depression, fatigue and total mood subscales. Both patients were diagnosed with insomnia.
Conclusion: This study found that subjective reports of daytime sleepiness and fatigue in head injury patients were not reliable and not well substantiated when compared with overnight polysomnographic sleep measures and physiologic tests of daytime sleepiness. The only association found was between low sleep efficiency and abnormally high scores on the tension, depression, fatigue and total mood subscales of the POMS. The overall abnormally high scores on the alexithymia scale, indicating poor emotional connectivity among our study patients, may provide an explanation for the lack of correlation between subjective and objective measures of daytime sleepiness.

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Nightly Variability in PLMS in Parkinsons Disease

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Introduction: Nightly variability in periodic leg movements in sleep (PLMS) has been demonstrated in elderly subjects without known neurodegenerative disease, however it remains uncertain whether such variability exists in a condition such as Parkinsons Disease (PD). We report here data from 27 PD patients studied polysomnographically for 3 consecutive lab nights.
Methods: Patients were 27 individuals diagnosed with idiopathic PD (X [SD] age = 60.7[10.9]; 19 M, 8 W) carrying a diagnosis of PD for a mean of 6.4 yrs. Patients were studied for 3 consecutive lab nights as initial drug free nights in a double-blind, placebo-controlled randomized trial. Parkinsonian medications were held constant across all 3 nights. Night 1 was a non-pill Baseline night. Nights 2 and 3 were single-blind, placebo run-in nights. Data for the current report are limited to only these 3 nights. PLMS were scored with conventional AASM criteria and corrected for Total Sleep Time (TST) to yield a PLMS Index (PLMSI).
Results: Although PLMSI was modestly reliable across nights (rho N1/N2 = .81; rho N1/N3 = .65; rho N2/N3 = .68), appreciable variability was noted. A difference in PLMSI of greater than 10 events per hour was seen in 4 patients from N1 to N2, in 6 patients from N2 to N3, and in 7 patients from N1 to N3. In 3 patients (11%), variability in excess of 25 events per hour was detected between at least one pair of nights. Indices were as likely to increase as decrease, with the exception being N1 to N2 where a trend for lower values were seen for N2 ($t = 2.01$, $p = .06$). Variability was unrelated to nightly variation in TST or Sleep Efficiency, thus arguing against overall sleep quality as the relevant factor.
Conclusion: These data show that, even among patients with a neurodegenerative condition involving widespread depletion of the dopaminergic system, PLMS are not constant from night–to–night. Factors underlying this within subject variance remain to be fully understood, but interventions attempting to treat such movements may be challenged by such inherent instability in this outcome and may require multiple nights of recording.

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REM Sleep Behavior Disorder in Parkinson's Disease

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Introduction: The aim of our study was to evaluate the frequency of REM sleep behavior disorder (RBD) related complaints in a group of patients with Parkinson's Disease (PD) and compare with a control group without PD.
Methods: Thirty four patients with PD and thirty seven non-PD controls were studied. Diagnosis of RBD related symptoms was performed by clinical history and Sleep Questionnaire. The patients had to answer three questions about RBD and were considered positive if two answers were "yes" . The authors compared PD group with the control group. Both groups answered questions about waking up out of the bed after an agitated dream, moving while dreaming and being observed moving while dreaming . We applied Chi-Square Test to our data.
Results: The mean age of the patients was 59.97±12.56 years in the control group and 61.34±8.68 years in the PD group, and the groups were similar by Chi-Square (p: 0.164). RBD related answers occurred in 10 patients (35%) in the control group and in 19 patients (65%) of the PD group. The difference between the groups was significant (p:0.018).
Conclusion: Our data show the higher frequency of RBD related complaints in a population with PD when compared with a control group without PD. In PD, REM sleep behavior disorderseems to be a common and potentially injurious condition that should be considered part of the clinical spectrum of the disease.

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Sleepiness Due To Wernicke's Encephalopathy Wirh Bilateral Hypothalamic Lesion In A 5-Year-Old Girl

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Introduction: Wernicke's encephalopathy (WE) is a severe neurological disorder caused by vitamin B1 deficiency. This disease is characterized by ocular symptoms, ataxia and mental confusion. We report a 5-year-old girl gradually developed sleepiness and diagnosed WE. The points of diagnosis on this case is the characteristic brain magnetic resonance imagings (MRI) findings. MRI revealed lesions in bilateral hypothalamus in addition to other lesions. She had sleepiness and bilateral hypothalamus lesions, so we measured hypocretin-1 level in cerebrospinal fluid (CSF). Hypocretin is reported to be markedly decreased in narcolepsy/cataplexy patients. Symptomatic narcolepy is caused by hypothalamic lesion such as strokes and tumors with decreased CSF hypocretin-1 levels. However, sleepiness without any other narcolepsy-related symptoms due to hypothalamic lesion has not been well documented. The aim of this study was to evaluate hypocretin-1 level in CSF due to hypothalamic lesion.

Methods: A patient presented sleepiness secondary to hypothalamic lesion was employed in the study. Hypocretin-1 level in CSF was measured using radioimmunassay kits (Phoenix Pharmaceuticals, Belmont, CA). Clinical symptoms, brain MRI and CSF hypocretin-1 level were correlated.

Results: Case Report: A 5-year-old girl gradually developed sleepiness and an abnormal sleep/wake schedule. After the onset, her sleep time was 15-20 hours per day and fell asleep frequently even while eating. On admission, her consciousness was almost clear, but gradually became impaired. She developed ocular symptoms (impairment of infraversion) and neurological symptoms (such as involuntary movements and hemiparesis and depression of speech and global confusional state). Brain CT revealed a low-density lesion involving thalamus, posterior hypothalamus. MRI revealed lesions in bilateral hypothalamus in addition to dorso-medial nucleus of thalamus and mammillary bodies and periaqueductal gray and floor of IV th ventricle. Electroencephalogram (EEG) revealed slow background activity (6-7Hz, 100-150microV) with sporadic appearance of posterior delta activities (2-3Hz, 130-150microV) during the awakening period. Prolonged sleep spindles (14 Hz, 130-150microV, 2-3 seconds duration) in dominantly frontal region were also observed during the sleeping period. Throughout EEG examination, she could not keep awake without being stimulated verbally. There were no abnormalities in auditory brainstem response. The level of vitamin B1 was low (38.7ng/ml). The level of hypocretin of CSF was decreased (<40pg/ml) compared to age matched controls (361 /-61pg/ml). Her sleepiness and MRI findings gradually improved with thiamine therapy. The sleep symptoms improved within 6 weeks and other clinical presentation also improved within 6-8 weeks and she was discharged 9 weeks later. Six months after the onset of sleepiness, both MRI lesion and CSF hypocretin level (158pg/ml) recovered to some degree. This case suggests that a dysfunction in the arousal state control relevant to hypocretin system may involve in some patients with WE.

Conclusion: Hypothalamic damage influences neuroendocrine functions, energy homeostasis, and sleep regulation. Decreased CSF hypocretin-1 may reflect degree of hypothalamic dysfunction, and it can explain the mechanism of sleep symptoms include sleepiness on this WE.

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Hypersomnia in POEMS is Associated with Plasma but not CSF Hypercytokinaemia

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Introduction: POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a severe, often fatal, multisystem disorder often associated with a plasma cell dyscrasia. A 37-year-old woman with a 2-year history of progressive, severe POEMS including IgA lambda and IgG kappa paraproteinaemias, anascara, premature ovarian failure, hyperprolactinaemia, and polyneuropathy was treated with an autologous stem transplant. No myeloma or plasmacytoma was found. All POEMS features resolved or improved except the IgG kappa paraproteinaemia, which persists. Two years later, she presented with sub acute onset hypersomnia including prolonged overnight sleeps of up to 14 hours and excessive daytime sleepiness (EDS) with 10 to 12 narcolepsy-like episodes of sudden onset sleep per day - including in inappropriate circumstances. We aimed to characterize the hypersomnia and investigate its pathogenesis.

Methods: We performed sleep studies including overnight video polysomnography (PSG) in hospital, multiple sleep latency tests (MSLT), and sleep questionnaires. Serum and cerebrospinal fluid (CSF) cytokines were measured by the relevant ELISA kits.

Results: Epworth Sleepiness Scale score 24. MSLT confirmed severe EDS with a mean sleep latency of 2.3 min (n = 4) without sleep onset REMs. Overnight video PSG in hospital was normal. Several daytime naps lasting 2 to 30 minutes were recorded and consisted of stage I usually followed by stage II sleep. Body mass index 20.4. Obstructive sleep apnoea absent. HLA DR2 negative. After an uninterrupted sleep of 8 hours, mean fasting plasma cytokine levels in serial samples taken at half hour intervals from 09 00 to 1300 h were all elevated compared with normal controls: tumour necrosis factor-α(TNF-α; 51.9 ± 5.5 pg/ml vs 13.9 ± 3.9; mean ± SEM vs 20 normal controls mean ± SEM); interleukin-6 (9.5 ± 1.9 pg/ml vs 1.5 ± 0.5), interferon-γ(22.7 ± 3.0 pg/ml vs 0 pg/ml), and interleukin-1β(IL-1β; 3.9 ± 1.3 pg/ml vs 1.1 ± 0.4). All cytokines were undetectable in the CSF. Circulating leptin, adiponectin, resistin, prolactin, growth hormone and thyroid hormones, and short synacthen test were all normal.

Conclusion: Both our report and characterization of increased non-REM sleep in POEMS are novel. The finding of plasma hypercytokinaemia - without any new endocrinopathy - suggests that cytokines may be contributing to the patient's excessive sleepiness. Raised plasma TNF-α and IL-1$\beta$are found in various human sleep disorders and they both enhance non-REM sleep when infused into animals. The absence of CSF cytokines in our patient may indicate that the effect of plasma hypercytokineamia on sleep is indirect or that any resulting CNS hypercytokinaemia is parenchymal and/or focal.

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A Case Of Acute Disseminated Encephalomyelitis Associated With Hypersomnia And Low CSF Hypocretin Levels

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Introduction: Hypocretin peptides have been demonstrated to be key molecules that control various hypothalamic functions. and have significant clinical relevance in sleep and neurological disorders. Hypocretin dysfunctions are reported in several symptomatic cases of narcolepsy or excessive daytime sleepiness (EDS) associated with neurodegenerative, surgical, ischemic and post-infectious insults to hypothalamus. We examined a case of a 7 year-old girl who was diagnosed as having acute disseminated encephalomyelitis (ADEM), and showed marked hypersomnia with a brain lesion in the bilateral hypothalamus, white matter and basal ganglia. CSF hypocretin levels were measured repeatedly during the course of illness and were correlated with the degree of EDS.
Methods: The CSF hypocretin levels were measured repeatedly along with the clinical course, by using radioimmnoassay.
Results: (Case) The young girl contracted a high fever and exhibited a generalized seizure accompanied by mild drowsiness 6 days later. Her consciousness level seemed to decline gradually, then transferred to Osaka Medical College hospital on the 14th day after the onset. On admission her vital signs were not remarkable, but she looked very sleepy and fell asleep easily. Neurological examinations revealed no focal signs. Further examinations of CSF indicate that the IgG index was slightly elevated and her myelin basic protein concentration was high. The serological viral titers were normal. A cranial MRI demonstrated a spotty bilateral lesion in the white matter, basal ganglia and hypothalamus. Diffuse high voltage slow waves were dominant in her EEG when she was subjectively awake, while a normal sleep EEG pattern was also seen when she behaviorally slept. Her total sleep time was approximately 22 hours daily. A nap sleep study indicated excessive sleepiness, as the total sleep time was 88.5% of the total dark time. Her sleep latencies were very short (2 minutes), but no REM sleep was observed at the sleep onset. The diagnosis of ADEM was based on her clinical symptoms associated with the white matter lesions and the elevated myelin basic protein in CSF. We initiated the steroid pulse therapy and resulted in gradual recovery. A nap sleep study showed marked improvement of sleepiness, as she did not fall a sleep during 20 minutes of the test. After 2 months of hospitalization, she was discharged. The neuroimages also showed substantial improvement one year after the discharge. (CSF hypocretin) The CSF hypocretin concentration on day 1 was reduced to 146 pg/ml, compared with the reported hypocretin level in healthy controls: 280.3 pg/ml. The hypocretin level gradually increased with the clinical course, 174 pg/ml on day 22, and 263 pg/ml on day 47 when she completely awake.
Conclusion: This is the first case report that demonstrated the CSF hypocretin levels were correlated with the degree of sleepiness in ADEM with hypothalamic lesion. Decreased hypothalamic hypocretin neurotransmission may be involved in the symptomatic case of hypersomnia associated with ADEM.

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Excessive Daytime Sleepiness And Low CSF Hypocretin-I (Orexin-A) Levels In A Patient Of With Probable Progressive Supranuclear Palsy

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Introduction: It has been reported that the level of cerebrospinal fluid (CSF) hypocretin-1 is low not only in subjects with narcolepsy but also in some neurological diseases with hypersomnia. Sleep disturbance has been mentioned as an occasional feature in patients with progressive supranuclear palsy (PSP), but the mechanism of sleep disturbance in patients with PSP was controversial. Here, we report the first case of hypocretin deficiency in a patient with probable PSP who showed excessive daytime sleepiness (EDS) without REM sleep disturbance.
Methods: Case: A 74-year-old Japanese woman. She developed difficulty in walking, falls and daytime sleepiness from two years ago. She often went to sleep during the conversation or medical examination and showed supranuclear vertical gaze palsy, mild rigidity in the neck and the bilateral arm, gait disturbance associated postural instability. She was diagnosed probable PSP by the NINDS-SPSP criteria (Neurology 1996; 47:1-9). Brain MRI showed the third ventricle was enlarged and midbrain tegmentum was atrophic. To examine the character of her sleep disturbance, polysomnography (PSG), multiple sleep latency tests (MSLT), Epworth sleepiness scale (ESS), human leukocyte antigen (HLA) test and measurement of level of CSF hypocretin-1 was performed.
Results: ESS was 19, MSLT showed short latencies (< 2 minutes), HLA testing was positive for DR2/DQB1, and CSF hypocretin-I concentration was undetectable (<40pg/ml). In the PSG study, sleep onset REM was not observed and the amount of stage 3-4 sleep remarkably increased (47% of total sleep time). In our patient, the treatment with methylphenidate HCl was effective on EDS.
Conclusion: Her EDS mimicked narcolepsy without cataplexy, because MSLT showed short latencies, HLA testing was positive for DR2/DQB1, and CSF hypocretin-I concentration was undetectable. In PSP, neurofibrillary tangles occurs in the hypothalamus, neuronal loss and gliosis are seen in a number of pontine and mesencephalic tegmental nuclei, substantia nigra, locus caeruleus. These neuropathological changes of PSP may cause decreased pre- or post-synaptic hypothalamic orexin neurotrasmission because orexin neurons are located in the hypothalamus and project widely to the forebrain and the brain stem. We would need to investigate the measurement of CSF hypocretin-I in more patients with PSP.

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Low Hypocretin-1 Levels In The Cerebrospinal Fluid Of Patients With Acute Traumatic Brain Injury

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Introduction: Complaints of excessive daytime sleepiness and other

sleep-wake-disturbances are common in the course after traumatic brain injury. We intended to test the hypothesis that a hypocretin-1 deficiency may be present in patients with acute traumatic brain injury.
Methods: Cerebrospinal fluid (CSF) hypocretin-1 levels have been determined in 24 patients (17 males, 7 females, mean age=36.9 years) with acute severe or moderate traumatic brain injury.
Results: In 19 patients (79%), CSF hypocretin-1 levels were abnormally low (<320 pg/ml; overall mean 190 pg/ml) compared to a healthy control group (n=20; mean 497 pg/ml).
Conclusion: Our finding of abnormally low hypocretin-1 levels in the cerebrospinal fluid in a majority of patients with acute severe or moderate traumatic brain injury was significant compared with an age-corresponding healthy control group. However, the pathophysiological, clinical and predictive significance of low CSF hypocretin-1 levels in acute traumatic brain injury is unclear at present time.

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REM Sleep Behaviour Disorder In Dementia: Preliminary Results In Clinically-Diagnosed Frontotemporal Dementia

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Introduction: The occurrence of REM sleep behavior disorder (RBD), characterized by motor activity, enacting dreams and persistent tonic EMG activity during REM sleep, has been reported in several different neurodegenerative diseases. Recent reports suggest a specific association with synucleinopathies (Parkinson disease, PD, multiple system atrophy, MSA dementia with Lewy bodies, LBD), rather than with non-synucleinopathies, such as Alzheimer disease (AD) and frontotemporal dementia (FTD) (Boeve BF et al., Mov Dis 2001;16:622-630. Boeve BF et al., Neurology 2003;61:40-45). However only one study (Boeve BF et al., Mov Dis 2001;16:622-630) aiming to assess the presence of RBD or REM without atonia (RWA) included patients with FTD: only 2/77 cases with a clinical diagnosis of FTD had a history suggestive of RBD, but none of the 6 cases that underwent polysomnography (PSG) showed RBD or RWA. The aim of this ongoing study is to evaluate by means of video-PSG a series of dementia patients, in order to establish the presence of RBD in non-synucleinoapthies, in particular FTD.
Methods: Up to date we studied 11 patients (6 F, 5 M; mean age 69.8 ± SD 8.5 years) with a clinical diagnosis of dementia, who underwent a complete video-PSG. Five met the clinical, neuropsychological and neuroimaging criteria for FTD (1 semantic dementia, 1 progressive nonfluent aphasia), 2 for probable AD, 1 for vascular dementia (VaD) and 3 for LBD. All the patients or relatives gave the informed consent for video-PSG, and in all but two (both with probable LBD) the recording was successful. Video-PSG included at least 8 hour-recording with EEG, EOG, EMG of submental and anterior tibialis muscles, oro-nasal flow, thoracic and abdominal efforts, and oximetry.
Results: Six out of eleven patients (1 with FTD, 1 with AD, 1 with VaD and 3 with probable LBD) had a history of nocturnal motor agitation during apparent sleep state, with vocalization and agitated behaviors suggestive of RBD. One out of 9 recorded patients (with a clinical diagnosis of LBD) had abnormal motor behavior during REM sleep and one (probable AD) had RWA at video-PSG. RBD or RWA were found in none of the other 7 patients. In particular, all the 5 FTD patients showed normal REM sleep characteristics, even the single case with a history suggesting abnormal motor agitation during sleep. Seven patients showed a number of periodic leg movements during sleep (PLMS) greater that 5 per hour, while only two patients had criteria for a diagnosis of obstructive sleep apnea (A+HI > 10). The two patients with a positive history of nocturnal motor agitation, and a clinical diagnosis of probable AD and VaD, had PLMS or/and sleep apnea (PLMS 35/hour and PLMS 92/hour with A+HI 34, respectively). Moreover, in the patient with VaD, a confusional arousal emerging from Non-REM sleep was recorded, whilst REM sleep was normal.
Conclusion: Our data confirm that RBD is not a typical feature of FTD, supporting its specific association with synucleinopathies. When motor agitation during the night is reported in patients with dementia, the differential diagnosis between RBD and other abnormal motor episodes or sleep disorders may be difficult. A full-night video-PSG, whenever possible, is mandatory for a correct diagnosis and treatment.

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Sleep Disorders Questionnaires and Cardiac Data in Patients with Strokes

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Introduction: Recent evidence links the risk of cerebrovascular disease with sleep apnea and snoring. Although the cardiovascular complications of sleep-related breathing disorders (SRBD) have been well documented and include hypertension (HTN), coronary artery disease (CAD), and arrythmias, the underlying mechanism for stroke remains unclear. The potential link of pre-stroke obstructive sleep apnea to cardiac abnormalities may provide helpful clues to this mechanism. We are investigating the association of cardiac data with the presence of SRBD in patients with strokes, using Sleep Disorders Questionnaires (SDQ).
Methods: We studied 50 patients who were admitted with documented ischemic or hemorrhagic strokes. Utilizing the sleep apnea portion of the SDQ and the Epworth Sleepiness Scale (ESS) questionnaires, information including age, gender, race, HTN, and body mass index (BMI) were obtained. An abnormal SDQ score was defined as > 32 for females and > 36 for males; ESS was defined as abnormal if > than 10. A BMI value of >27.3 Kg/M2 was considered abnormal. Additionally all patients underwent 2D echocardiography, measuring ejection fraction (EF%), presence of left ventricular hypertrophy (LVH), diastolic dysfunction (DD), dilatation of the left atrium (LA), aortic sclerosis (AS), aortic regurgitation (AR), and aortic atherosclerosis (AAth).
Results: The average age of the subjects was 64 yo (range 26-90); 33 males and 17 females. 46 of the 50 patients had ischemic strokes and 4 were hemorrhagic. The average SDQ score was 33 (range 16-48, SD 8). The average ESS was 10 (range 0-24, SD 7). Mean BMI was 29 (range 17-53). 8 of the 17 females (47%) and 15 of the 33 males (45%) had abnormal SDQ scores. Significant correlation between SDQ scores and gender, BMI, ESS scores and presence of HTN ($r = 0.47, 0.43, 0.40, 0.60$; $p < 0.05$) were found. However, echocardiographic data (EF, LVH, DD, dilatation of LA, AS, AR, and AAth) did not correlate with the SDQ or ESS scores.
Conclusion: These findings demonstrate that patients with stroke have frequent complaints of preexisting SRBD. However these complaints do not correlate with features of cardiac disease as assessed by echocardiography. The connection of sleep apnea to cardiac dysfunction precluding stroke may not be evident on conventional echocardiography. Therefore, other mechanisms may play a role in the predisposition of sleep apnea patients to cerebrovascular disease.

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The Use of Medications, Herbs, Natural Products and Complementary and Alternative Practices and Products (CAPPs) in Persons with Restless Legs Syndrome

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Introduction: People with RLS deal daily with symptoms of sleep disturbances, discomfort, and fatigue which affect occupational activities, social activities and family life. The symptoms progressively worsen with age, with temporary relief from medications that only treat the symptoms of the syndrome. Complementary and alternative practices and products (CAPPs) may be used to assist in controlling symptoms. Use of CAPPS has not been identified in RLS patients. Given the inconsistent outcomes with conventional treatment, it is believed that persons suffering with RLS are seeking adjunctive therapies. The main objective of this study was to examine the use of pharmacological interventions, biologically-based therapies, and other CAPPs in persons with RLS.
Methods: A convenience sample of 40 adults, 9 men and 31 women, were recruited from persons with RLS who attended three different RLS support groups. During a single session, data was collected on demographics (age, marital status, ethnicity, employment status, education), medical history (age at RLS diagnosis, years since diagnosis, family history of RLS, co-morbid conditions), and reported use of pharmacological interventions, biologically-based therapies, and other CAPPs.
Results: The mean age of participants was 66 (SD = 10.5) with a mean age of 49 (SD = 21) at time of RLS diagnosis. Half of the participants had a positive family history for RLS including five participants with rheumatoid arthritis. The most common co-morbid medical conditions were hypertension, iron deficiency, and neuropathy. Sixty-five percent of the total sample reported using CAPPs, with a mean of 2.5 biologically-based CAPPs and 0.9 other CAPPs used. The most commonly used biologically-based CAPPs were Vitamins E, C, B and multivitamins (MVI). Other commonly used CAPPs included prayer, exercise, meditation, and music. Current CAPP use was associated with past CAPP use ($r = .50$, $p = .001$) and marginally associated with education ($r = .31$, $p = .055$). Current CAPPs use was also associated with comorbid illnesses ($r = .46$, $p = .03$) while use of prescription medications was inversely associated with years since diagnosis of RLS ($r = -.318$, $p = .049$).
Conclusion: This study suggests a high prevalence of CAPPs use among persons with RLS to decrease symptoms that are unmanageable by conventional pharmaceutical interventions. Further research is necessary to clearly define patterns of CAPP use among persons with RLS and to evaluate the efficacy of these therapies in controlled clinical trials.

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Daytime Sleepiness and Fatigue in Relapsing Remitting Multiple Sclerosis (RRMS) During 12-Month Therapy with Interferon β 1a

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Introduction: Fatigue and daytime sleepiness are common complaints in patients with multiple sclerosis. There still is no common explanation for theses symptoms. Amantadine and modafinil are often used for therapy. In clinical trials the Expanded disability Status Scale (EDSS) assesses disability. As an ordinal scale it is heavily biased to loco motor function, however. The NMSS Task Force introduced the MS Functional Composite (MSFC). The present study investigates the influence of the disease modifying drug interferon β 1a (AVONEX ®) on fatigue, sleepiness, physical and cognitive functions measured by different scales in RRMS.
Methods: 14 patients with RRMS (6 men, 8 women, age: 33.9 ± 9.8 years) and 17 healthy controls (5 men, 12 women, age: 30.0 ±9.2 years) were investigated with the following instruments: 1. Extended Disability Status Scale (EDSS) 2. MS Functional Composite (MSFC): ambulation (Timed 25 Foot Walk, T25W), arm function (9 Hole Peg test, 9 HPT) and cognitive function (Paced Auditory Serial Addition Test, PASAT (3 min version) were investigated The number of correct sums given in the PASAT (out of 60 possible), the mean time in seconds of two T25W trials and the mean time in seconds across four 9HPT trials (two with the dominant and two with the non-dominant hand) were used for analysis. 3. Fatigue Severity Scale (FSS by Krupp et al.) Estimation of fatigue in various situations with severity from 1 to 7 4. Epworth Sleepiness Scale (ESS)
Results: EDSS declined significantly after 12 months (1.7 ± 0.9 vs. 0.9 ± 1.0, p<0,01). PASAT results rose significantly (39.9 ± 12.6 vs. 47.3 ± 8.3, $p < 0.5$). Controls showed no changes of the MSFC results. Score of the Fatigue Severity Scale was significantly raised in patients compared to controls before starting therapy (29.8 ± 10.9 vs. 22.0 ± 7.8, $p < 0,05$). There was no difference during follow-up. Epworth Sleepiness Scale significantly declined at month 12 (4.4 ± 4.2 vs. 7.0 ±3.6 in controls, $p< 0.05$) with no difference at the first and second investigation. After 12-month treatment FSS correlated with improved arm function (9HTP, r: 0.89, $p< 0.01$) and cognitive function (PASAT, r: -0.89, $p< 0.01$)
Conclusion: Fatigue occurs in up to 80% of MS patients. Therapy is mainly symptomatic. Though interferon β 1a may worsen fatigue during the first applications the present study demonstrates an improvement of fatigue and sleepiness over 12-month therapy. Disease course improved as shown by EDSS and MSFC-results. As fatigue improvement correlated to MSFC results this symptom seems to be related to demyelinisation. Interferonβ 1a should also be considered for causal treatment of fatigue in rrMS.

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Comparison of Patient Characteristics for Development or Improvement in Obstructive Sleep Apnea with Vagus Nerve Stimulation

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Introduction: Vagus nerve stimulators (VNS) are current treatment for medically refractory seizures. Some literature suggests that VNS has effects on the respiration of sleep causing sleep apnea and excessive daytime sleepiness. The apnea-hypopnea index (AHI) can increase in patients treated with VNS, but in others, it may remain unchanged. Predicting who will develop sleep-related breathing complications and who will not is currently not possible. The purpose of this study is to determine if there are characteristics of the patient's epilepsy or epilepsy treatment that influence respiratory response to VNS.
Methods: To examine the relationship between VNS and respiration during sleep, we retrospectively reviewed the polysomnographic tracings of 27 epilepsy subjects who consented to undergo routine polysomnography before and after VNS treatment. 2 patients were elim-

inated secondary to having a seizure during a sleep study. 25 patients (ages 19-56, X=35, Sd=13, M=14, F-11) were reviewed.
Results: The AHI of 6 patients worsened with VNS stimulation by 10 or more points while 5 patients improved by the same margin. The remaining 14 patients had AHI changes of less than 10 points. Of the 6 patients that showed worsening of their AHI, 4 had bilateral epileptiform activity (3 bi-frontal, 1 bi-temporal). One other individual had >90% right temporal spikes with <10% in the left frontotemporal region. The source of epileptiform activity in the final individual remains unknown. Conversely, all patients who demonstrated an AHI improvement had unilateral temporal epileptiform changes, with 3 of the 5 being left temporal. No clear patterns emerged between particular anti-epileptic drug usage and AHI improvement or worsening.
Conclusion: VNS represents a relatively new treatment modality for epilepsy. The effect of VNS on sleep parameters is largely unknown and their mechanisms of action on sleep are even more obscure. This preliminary study raises the issue of underlying epilepsy type and localization being a factor that might determine a patient's respiratory outcome from VNS treatment. Further investigation into this and other patient variables such as concurrent medication usage might allow physicians to predict and anticipate which patients are at increased risk to develop sleep-related respiratory difficulties.

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Subjective Sleepiness May Identify Pre-Stroke White Matter Disease In Patients with Acute Stroke

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Introduction: Sleep Disordered Breathing (SDB) is a risk factor for cardiovascular disease. SDB is associated with hypertension, a common risk factor for cerebrovascular disease. Although SDB is more prevalent immediately following a stroke, it remains unclear whether SDB may be an independent risk factor for stroke. White matter disease (WMD) has been associated with hypertension and increases the risk for recurrent stroke. Recent data suggest an independent association between SDB and WMD. Since most patients with a new diagnosis of stroke or transient ischemic attack (TIA) undergo brain magnetic resonance imaging (MRI), measuring the degree of WMD may present a new opportunity to predict future disease. Furthermore, if SDB increases the likelihood of pre-stroke white matter disease, treating patients with sleep apnea may help prevent stroke recurrence. We studied the presence of SDB prior to stroke and degree of white matter disease.
Methods: All patients admitted to the Stroke Treatment and Prevention Unit during a six week period, with a diagnosis of stroke or TIA, were invited to participate. Informed consent was obtained and each subject (or next-of-kin, not necessarily bed partner) completed the Epworth Sleepiness Scale (ESS) and the Sleep Apnea portion of the Sleep Disorders Questionnaire (SA-SDQ), two validated measures of SDB. Subjects were asked to answer the questionnaire based on their experiences during the week(s) prior to the stroke/TIA. We used previously documented cutoffs known to correlate with obstructive sleep apnea syndrome: ESS greater than 10 and SA-SDQ greater than or equal to 32 in women and 36 in men. After reviewing all brain imaging, we excluded subjects who did not undergo MRI. Periventricular and subcortical WMD on FLAIR MRI was scored using previously validated Manolio and Fazeka scales, higher scores correlating with more severe WMD. We also collected data including age, gender and history of hypertension.
Results: Fifty two subjects with a diagnosis of stroke/TIA completed the ESS, SA-SDQ and MRI. 28 patients were younger than 65 years. Using the Mann-Whitney U-test we found that age remains a good predictor of WMD (p=0.004 Fazeka; p=0.002 Manolio). We further found no association between SA-SDQ or ESS and Fazeka scores (p=0.233; p=0.133) or Manolio scores (p=0.368; p=0.891). High SA-SDQ scores were found in 93.5% of the hypertensive subjects but only 58.3% of the non-hypertensive subjects (p=0.003 Fisher's Exact test). In all subjects under age 65, there was a trend toward an inverse relationship between sleepiness scores and Fazeka score (p=0.072). However, of the 13 non-hypertensive subjects in this group, there was a trend to WMD with higher sleepiness scores.
Conclusion: These data suggest a correlation between a history of hypertension and SA-SDQ in patients with acute stroke. The ESS and SA-SDQ may be helpful to identify pre-stroke WMD in patients under 65 years, but should be better validated for use in acute stroke patients. Previously documented correlation of WMD and age is supported in this group of patients with acute stroke.

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A Case Of Acute Disseminated Encephalomyelitis Associated With Hypersomnia And Low CSF Hypocretin Levels

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Introduction: Hypocretin peptides have been demonstrated to be key molecules that control various hypothalamic functions. and have significant clinical relevance in sleep and neurological disorders. Hypocretin dysfunctions are reported in several symptomatic cases of narcolepsy or excessive daytime sleepiness (EDS) associated with neurodegenerative, surgical, ischemic and post-infectious insults to hypothalamus. We examined a case of a 7 year-old girl who was diagnosed as having acute disseminated encephalomyelitis (ADEM), and showed marked hypersomnia with a brain lesion in the bilateral hypothalamus, white matter and basal ganglia. CSF hypocretin levels were measured repeatedly during the course of illness and were correlated with the degree of EDS.
Methods: The young girl contracted a high fever. Six days after affliction, she was admitted and exhibited generalized seizures accompanied by mild drowsiness. Her consciousness level seemed to decline gradually, then transferred to Osaka Medical College hospital on the 14th day after the onset of the febrile episode. Her vital signs were not remarkable, however she looked very sleepy and fell asleep easily. Neurological examinations revealed no focal signs. Further examinations of CSF indicate that the IgG index was slightly elevated and her myelin basic protein concentration was high. The serological viral titers were normal. A cranial MRI demonstrated a spotty bilateral lesion in the white matter, basal ganglia and hypothalamus. Diffuse high voltage slow waves were dominant in her EEG when she was subjectively awake, however a normal sleep EEG pattern was also seen when she behaviorally slept. Her total sleep time was approximately 22 hours daily. A nap sleep study indicated excessive sleepiness, as the total sleep time was 88.5% of the total dark time. Her sleep latencies were very short (2 minutes), but no REM sleep was observed at the sleep onset.
Results: The diagnosis of ADEM was based on her clinical symptoms associated with the white matter lesions and the elevated myelin basic protein in CSF. We initiated the steroid pulse therapy and resulted in gradual recovery. A nap sleep study showed marked improvement of sleepiness, as she did not fall a sleep during 20 minutes of the test. After 2 months of hospitalization, she was discharged. The neuroimages also showed substantial improvement one year after the discharge. The CSF hypocretin concentration on day 1 was reduced to 146 pg/ml, compared with the reported hypocretin level in healthy controls: 280.3 pg/ml. The

hypocretin level gradually increased with the clinical course, 174 pg/ml on day 22, and 263 pg/ml on day 47.

Conclusion: Recently, several clinical studies also suggested that the disruption of the hypothalamic hypocretin system in various neurological conditions might result in secondary EDS. Von Economo reported a number of EDS cases associated with encephalitis lethergica. The detailed pathological examination of these cases indicated an involvement of the thalamus and hypothalamus pathology. In our case, EDS was associated with acute lesions in the bilateral hypothalamus with the preceding febrile episode. Interesting to note that clinical symptoms of our case resembles that of a "somnolenet-opthalmorgic form" of encephalitis lethergica by von Economo.

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Sleep, Depression and Quality of Life in Coronary Artery Disease Patients

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Introduction: Sleep was shown being disturbed in cardiac pathology; while disturbed sleep have negative impact to development of the latter. From the other hand, depression and anxiety have direct impact disturbing sleep, developing cardiac diseases and reducing quality of life (QoL). The objectives were an investigation of sleep quality, anxiety, and depression in coronary artery disease (CAD) patients in relation to their functional state and quality of life (QoL).
Methods: Polysomnography was used for objective evaluation of sleep quality. Subjective sleep quality was assessed using Pittsburgh sleep quality questioner. Anxiety and depression was evaluated by Hospital Anxiety and Depression Scale. Short Form 36 was used for assessment of QoL. The contingent was 50 healthy subjects and 1086 CAD patients: NYHA functional class I was in 49 pts, class II in 627 pts; and class III in 405 pts. Four randomised groups according cardiovascular status were distinguished: without anxiety and depression (465 pts), with anxiety (229 pts); with depression (64 pts), and with both, anxiety and depression (171 pts). Patients with sleep apnoea syndrome (AHI>15) were excluded from the investigation.
Results: CAD pts, as compared with healthy subjects, demonstrated reduced TST, SE, REM and 3-4 sleep stages as well as increased WASO. Subjective quality of sleep, measured by PSQI, was worse in CAD pts, also. Worsening of sleep quality was followed lowering functional state in CAD pts. Hypertension was followed by reduced TST, SE, and non-REM sleep, while diabetes, heart failure and frequent HR disturbances - additionally by a reduced REM sleep. Leading pathology and complications were followed by a worsening of objective sleep quality: hypertension - by a decrease of TST, SE and 3-4 sleep stages, while diabetes, heart failure and frequent premature beats - additionally by a reduction of REM sleep. Subjective sleep was gradually decreased with worsening of functional status and developing of leading pathology and complications. Objective sleep quality was worse in pts with frequent premature beats, especially ventricular ones, as compared with pts showing supraventricular premature beats. They demonstrate decreased SE, REM sleep, and 3-4 sleep stages as well as increased WASO. However, subjective sleep quality measured by PSQI was better in patients with frequent ventricular premature beats, as compared with patients displaying supraventricular ones. Depression alone, or depression and anxiety being together were followed by worsening objective sleep quality, while anxiety alone - by worsening subjective sleep quality, as well as in patients with both, anxiety and depression. Quality of life, especially mental one, was reduced in patients with anxiety, as compared with patients having depression, and with both, anxiety and depression.
Conclusion: CAD and its complications were disturbing sleep quality measured by objective and subjective parameters as well as QoL. Anxiety was related to worsening subjective sleep quality, while depression - to changes in sleep structure and reduced TST. Anxiety and depression or both symptoms impaired QoL in CAD patients.

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Sleep Quality and Patterns in Tracheostomised, Chronically Ill Subacute Care Patients

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Introduction: Introduction: Sleep disturbances are common in hospitalized patients. The sleep schedule, pattern and quality are dependent upon multiple factors. Patient clinical status, pain and discomfort, effects of the medications, relative lack of environmental clues and staff activity are generally responsible for poor sleep quality. In addition, level of noise, ventilator, intravenous and feeding pump alarms disturb the sleep. Tracheostomy not only causes discomfort and inconvenience, the management of secretions becomes difficult, frequently interrupting the sleep. This study documents the sleep quality and patterns in this special and increasing subset of patients
Methods: Methods: National Sleep Foundation Sleep Diary was used to document the sleep schedule, quality and patterns for two consecutive weeks. Thirty two patients were selected based on their ability to provide responses, recollection of previous night events and consent to participate in the study. Patients were recruited in three sub-acute units. All participants had a tracheostomy, a percutaneous gastrostomy tube for feedings, analgesics and anxiolytic medications for last many weeks. The daytime activity was limited to their rooms, brief physical and occupational therapy and in general sedentary life style.
Results: Results: Out of the cohort of 32 patients 10 were women and 22 men. Mean age was 57+9 years. Median length of hospitalization was 13+6.7 months. Average bedtime was between 7:30 pm to 10 pm. Wake times ranged from 5 am to 10 am. Variable sleep latencies from 10 minutes to 3 hours were noted. Most patients (65%) reported 4 to 8 awakenings during the night. Physical discomfort, voiding, tracheal-suctioning and noise disturbed the sleep. Most patients felt that they slept for 5 to 10 hours and woke up somewhat refreshed or fatigued. Patients did not consume caffeinated drinks, nor had alcohol or heavy meals. Most patients received limited physical therapy for exercise and took multiple medications. Almost all took anxiolytic, hypnotic and analgesics through out the day. Patients sat at the edge of the bed, prayed or watched television about one hour prior to sleep.
Conclusion: Conclusions: Chronically hospitalized, subacute care patients have variable sleep latencies and multiple awakenings throughout the night. Their sleep efficiency and sleep architecture is not known due to lack of studies in this population. Recommendations can be made to improve the sleep quality of these patients.

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Subjective Reports of Sleep Quality, Sleepiness and Fatigue among Dyspepsia Patients

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Introduction: The diagnosis of dyspepsia is based on consensus symptom criteria (including gastric pain, acid reflux, bloating, etc) and may be diagnosed without the presence of an organic explanation. It has been postulated that dyspepsia patients may experience general somatization and thus may complain of symptoms of poor sleep and fatigue. The goal of this study was to determine whether disturbed sleep characteristics determined by self report questionnaires are present among a group of dyspepsia patients. Another aim of our study was to assess the prevalence of self-reported daytime sleepiness and fatigue in this sample of patients.
Methods: A total of thirty-six patients (twenty-six women and ten men) with dyspepsia who were taking prescription medication for their condition from two urban centers (Toronto and Montreal) participated in the study. To determine the severity of dyspepsia, patients were asked to report symptoms they experience from a checklist; rate their most bothersome symptoms; and describe the level of concern they experience in regards to their dyspepsic symptoms on a likert scale from 0-3, 0 being: not at all concerned and 3 being: very concerned. In addition, sleep disturbance was assessed by the Pittsburgh Sleep Quality Index (PSQI),

daytime sleepiness was determined by the Epworth Sleepiness Scale (ESS) and fatigue was described by the Fatigue Severity Scale (FSS).
Results: Using the PSQI, it was determined that 94% (29/31) of patients experienced poor sleep quality. Fifty-six percent (20/36) of patients experienced clinically significant daytime sleepiness. Further, 56% (20/36) of patients experienced clinically significant daytime fatigue. There was a weak, non-significant correlation between the number of symptoms of dyspepsia experienced and subjective sleepiness and fatigue. In addition, no correlation existed between the patients' level of concern with their dyspepsic symptoms and subjective reports of sleepiness and fatigue.
Conclusion: The prevalence of self-reported poor sleep quality was high and subjective complaints of daytime sleepiness were also increased in the dyspepsic sample. Fatigue as reported by the FSS was also more frequent among the dyspepsia patients. The dyspepsia symptoms experienced by these patients did not account for their poor sleep quality, daytime sleepiness or fatigue. Further studies need to be conducted to determine whether subjective complaints of poor sleep are reflected in physiologic measures of sleep.

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Sleep as a Behavioral Self-Management Intervention for Headache
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Introduction: The association between chronic pain and sleep disturbance has been well-documented in the literature. In particular, chronic pain sufferers often complain of difficulty initiating and maintaining sleep. Research on the etiology of this sleep disturbance has found evidence for EEG abnormalities (i.e., alpha-intrusion), pre-sleep cognitive arousal, and co-morbid depression as potential mechanisms of sleep disturbance. Little attention has been given to examining pain behavior that is maladaptive for sleep hygiene. Although stimulus control and sleep restriction have been recommended to treat sleep disruption among chronic pain sufferers, no study has reported on the specific behaviors associated with poor sleep in this population. Headache is one form of chronic pain that is associated with sleep disturbance. Early studies on headache and sleep have found that sleep can relieve a migraine attack. Given the dearth of literature on pain behaviors that affect sleep, the present study examined the use of behavioral self-management interventions reported by a sample of tension-type headache sufferers and the implications for sleep hygiene.
Methods: Data were analyzed for 27 females meeting criteria for tension-type headache. The average age was 19.3 years (SD = 2.50). The ethnic composition of the group was 70% Caucasian, 15% African-American, and 15% other. Self-reported data were collected from a pain history questionnaire packet as part of a psychophysiological assessment on headache pain. The packet included a list of self-management interventions with questions on the use of the intervention, the frequency of use, and the effectiveness of the intervention.
Results: The results revealed that "go to sleep" was the most utilized self-management intervention, with 82% of headache sufferers reporting its use. A Wilcoxon Signed Rank Test revealed that "go to sleep" was utilized significantly more ($p < .05$) than all other interventions except "distract self". With regard to frequency, 28% reported using sleep "every time" or "always", 33% reported using it "most of the time" or "often", and 33% reported using it at least three times per week. Finally, sleep was rated as the most effective intervention. A two-tailed, paired-samples t-test revealed that "go to sleep" was rated as significantly more effective ($p < .05$) than hot compress, cold compress, having a drink, and distracting self.
Conclusion: The present data indicate that sleep is the most utilized self-management intervention reported by the headache sufferers in this study, with the majority of headache sufferers reporting frequent use of sleep to relieve a headache attack. In addition, headache sufferers rated sleep as the most effective intervention. The frequency and effectiveness of sleep as a self-management intervention is likely to have strong reinforcing properties for pain relief, but the behavior will lead to decreased regularity of the sleep-wake schedule. An erratic sleep-wake schedule has been associated with insomnia. These findings are consistent with the hypothesis that sleep-seeking behavior among headache sufferers may precipitate or perpetuate insomnia.

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Sleep Duration and Health in Breast Cancer
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Introduction: Health-care professionals commonly encounter complaints about insufficient sleep. While it is unclear how many hours of sleep per night are optimal, extremes in sleep duration have been linked with poorer health outcomes in patient and general populations. We wondered how sleep duration would relate to physical and mental health in breast cancer survivors.
Methods: Participants were 2933 women (age 28-74 years) participating in the Women's Healthy Eating and Living (WHEL) Study, a randomized trial of the effect on breast cancer progression of a dietary pattern that emphasizes micronutrients and phytochemicals. The women were within 4 years of diagnosis of early stage (Stages I (≥ 1cm), II, IIIa) breast cancer and completed a Thoughts & Feelings questionnaire (adapted from the Women's Health Initiative (WHI)) prior to participation in the WHEL Study. This paper focuses on health-related quality of life (HRQOL) using the RAND-36 Health Survey (rated 0-100, higher scores indicate better functioning; 5-point differences are clinically meaningful); psychological distress using the Center for Epidemiologic Studies-Depression Scale 8-item screening form (CESD-sf: logarithmic scoring, range=.001-.912; scores ≥ 0.06 indicate clinically significant distress); sleep disturbance (WHI Insomnia Rating Scale); daytime sleepiness (frequency of naps and falling asleep during quiet activities: 0, 1, 2, 3, 4, ≥ 5 times/week). Sleep duration was assessed with the following question: About how many hours of sleep did you get on a typical night during the past 4 weeks (≤5, 6, 7, 8, 9, ≥ 10 hours). Body mass index (BMI) was calculated as kg/m2 (normal=18.5-24.9; overweight=25.0-29.9; obese=30.0+). Data were analyzed using SPSS 11.0 multiple analysis of variance with sleep duration as the categorical variable.
Results: Significant sleep duration differences emerged for all measures ($p \leq .001$). Post-hoc analyses revealed the following: sleep duration of 7-8 hours was associated with better RAND-36 physical health (≤5hrs=61, 6hrs=73, 7hrs=77, 8hrs=77, 9hrs=74, ≥ 10hrs=68) and mental health (≤5hrs=63, 6hrs=73, 7hrs=79, 8hrs=78, 9hrs=73, ≥ 10hrs=69); 6-8 hours was associated with lower CESD-sf distress (≤5hrs=.129, 6hrs=.055, 7hrs=.040, 8hrs=.044, 9hrs=.066, ≥ 10hrs=.119) and lower BMI (≤5hrs=29.3, 6hrs=27.1, 7hrs=26.7, 8hrs=26.8, 9hrs=28.0, ≥ 10hrs=29.2); 6-7 hours was associated with less sleep disturbance ((≤5hrs=12.68, 6hrs=10.74, 7hrs=10.96, 8hrs=11.97, 9hrs=14.18, ≥ 10hrs=17.40) and lower frequency of falling asleep during quiet activities (≤5hrs=2.52, 6hrs=2.25, 7hrs=2.46, 8hrs=2.54, 9hrs=2.78, ≥ 10hrs=2.71); 8-9 hours was associated with less-frequent naps (≤5hrs=2.04, 6hrs=2.10, 7hrs=2.08, 8hrs=1.86, 9hrs=1.92, ≥ 10hrs=2.03).
Conclusion: In terms of physical and mental HRQOL, women breast cancer survivors who averaged 7-8 hours of sleep per night reported bet-

ter functioning. By comparison, those reporting ≤5 or ≥ 10 hours had lower physical HRQOL and those reporting ≤7 or ≥ 8 hours had lower mental HRQOL. These differences exceeded the 5 point threshold on the RAND-36 and, thus, were deemed clinically significant. Women averaging ≤5 or ≥ 9 hours of sleep reported mean CES-D scores which exceeded the 0.06 cutoff. This indicates the presence of clinically significant psychological distress and suggests the possibility of a diagnosable mood disorder. Those women were also in the upper range of the overweight category. Somewhat shorter sleep duration (6-7 hours) was associated with less propensity to fall asleep during the day and less sleep disturbance, while 8-9 hours was associated with the fewest naps. Depending on the outcome of interest, optimal sleep duration may range between 6 and 8 hours per night in breast cancer survivors. However, apart from napping, there was no measure by which those reporting 8 hours of sleep appeared significantly healthier than those reporting 7 hours of sleep.

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Light Exposure And Reported Sleep, Mood, Functional Performance, And Quality Of Life In Breast Cancer

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Introduction: Breast cancer patients undergoing chemotherapy have many distressing complaints such as poor sleep, lack of energy, decreased daily functioning, and fatigue. As a part of a larger ongoing study, we previously reported that breast cancer patients were exposed to lower bright light during their first week of chemotherapy compared to baseline, and this decrease was associated with increased fatigue. Here we report findings on the relationship between light exposure and sleep, depression, functional performance and quality of life.

Methods: 64 women (mean age 51.7, SD 10.4, range 34-79 yrs) diagnosed with stage I-IIIA breast cancer and scheduled to receive 4 cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy were included. Light exposure (lux) was measured with Actillumes (Ambulatory Monitoring, Inc., Ardsley, NY), worn for 72 consecutive hours before (week 0) and during the first week (week1) of chemotherapy. Only out-of-bed (start and stop times based on patients' diaries) lux data were used. The Pittsburgh Sleep Quality Index (PSQI), the Center for Epidemiological Studies Depression Scale (CES-D), the Functional Outcomes of Sleep Questionnaire (FOSQ), and the Functional Assessment of Cancer Therapy-Breast (FACT-B), were administered during week 0 and week1. Women were divided into two groups: greater than (group 1) and less than (group 2) 60 minutes of bright light (>1000 lux) exposure per day.

Results: From week 0 to week 1, mean light exposure decreased significantly (489.7 vs. 283.6 lux, F=5.60, p=.02). In week 0, those in group 2 reported worse sleep than those in group 1 (PSQI total scores: Mean=7.8, SD=3.5; vs. Mean=5.5, SD=3.4; p=.01). In week 1, in addition to again reporting poor sleep (PSQI total scores: Mean=8.6, SD=4.1; vs. Mean=5.7, SD=2.0; p=.00), those in group 2 compared to group 1 also reported more depressive symptoms (CES-D total scores: Mean=16.6, SD=13.7; vs. Mean=9.3, SD=7.2; p=.02), lower daytime function (FOSQ activity level factor scores: Mean=3.03, SD=0.6, vs. Mean=3.5, SD=0.5; p=.01), and worse general quality of life (FACT-B general scores: Mean=73.1, SD=16.7; vs. Mean=84.3, SD=14.3; p=.03). In both week 0 (r=-0.27, p=0.04) and week 1 (r=-0.36, p=0.01), lower amounts of bright light exposure was significantly correlated with worse sleep. In week 1, lower bright light exposure was correlated with lower daytime function (r=0.36, p=0.01) and worse quality of life (r=0.29, p=0.03).

Conclusion: Patients with less bright light exposure reported more sleep problems, both before and during chemotherapy, suggesting that the sleep disturbance was not just a side-effect of chemotherapy. Compared to baseline, patients were exposed to lower bright light exposure during their first week of chemotherapy, and those with lower light exposure reported worse sleep, more severe depression, lower functional performance and poorer quality of life. Previous studies have shown that increased light exposure improves both sleep quality and mood. Although the cause and effect of light exposure and functional performance can not be determined in this study, increasing breast cancer patients' light exposure during chemotherapy may improve sleep quality, depressive symptoms, daily functioning and quality of life.

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Sleep And Its Relationship To Vascular Endothelial Growth Factor In Response To Standardized Chemotherapy In Breast Cancer

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Introduction: Sleep disturbances are a common and distressing complaint in women with breast cancer, particularly during chemotherapy. There has been a concerted effort to identify underlying biochemical factors associated with these sleep disturbances. The angiogenic peptide vascular endothelial growth factor (VEGF) is elevated in the peripheral circulation of women with breast cancer. It is a powerful prognostic biomarker, with elevated levels predicting poorer response to therapy and poorer survival. Few studies have examined the effects of chemotherapy on VEGF nor its possible relationship with disturbed sleep.

Methods: Twenty-six women (age range 32-79 years) diagnosed with stage I-IIIA breast cancer were studied. Sleep variables total sleep time (TST) and wake after sleep onset (WASO) were determined with wrist actigraphy (Actillume II, Ambulatory Monitoring, Inc, Ardsely, NY), a validated device that measures movement and from which sleep/wake can be distinguished. VEGF levels (via ELISA) were determined prior to and following cycle 1 and cycle 4 of adjuvant or neoadjuvant anthracycline-based chemotherapy.

Results: Chemotherapy led to a significant increase in the amount of daytime TST (F=10.0, p=0.006). Compared to pre-chemotherapy [75.8 pg/ml, SD=93], VEGF levels were significantly elevated at cycle 4 of chemotherapy [138 pg/ml, SD=102] (F=9.2, p=0.006). The elevated VEGF levels were positively correlated with daytime (r=0.561, p=0.008) and negatively correlated with nighttime (r=-0.511, p=0.003) TST. VEGF levels were positively correlated with daytime (r=0.571, p=0.03) and nighttime (r=0.615, p=0.001) WASO.

Conclusion: Standard adjuvant or neoadjuvant chemotherapy lead to elevated levels of VEGF, an important biomarker that corresponds to inflammation. The elevated VEGF levels were associated with poorer sleep during chemotherapy treatment. These novel findings are promising in that they suggest that 1) chemotherapy leads to a generalized increase in inflammation in women with breast cancer and 2) that this

increased inflammation may be associated with poorer sleep. The findings add to recent behavioral studies linking elevated VEGF levels with poorer well being in cancer patients.

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Characteristics of Nocturnal Sleep Related with Clinical Parameters in Hemodialysis Patients with Excessive Daytime Sleepiness

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Introduction: It has been reported that excessive daytime sleepiness (EDS) is a very common problem in the patients with chronic renal failure (CRF) that receive hemodialysis (HD). Although Primary sleep disorders such as sleep apnea syndrome (SAS), restless leg syndrome (RLS), and periodic limb movements of sleep (PLMS) have been suggested as the causes of EDS in hemodialysis patients, nocturnal sleep parameters related with their important clinical factors has not been clearly defined. We aimed to illustrate any relationship of essential clinical parameters in hemodialysis patients with sleep parameters from the nocturnal polysomnographic studies (NPSG).
Methods: The Epworth Sleepiness Scale (ESS) was administered in 38 patients (26 males, 12 females; median age 49 years) with chronic renal failure who have been receiving the hemodialysis for more than 3 months in Kangwon National University Hospital. The mean score (SD) of ESS was 8.3 (5.6). In nine patients (6 males, 3 females; median age 47 years) among 11 patients with ESS score above 10, overnight polysomnographic studies were done. We did the correlation analysis between clinical laboratory parameters and objective sleep parameters from the NPSG.
Results: Among 9 patients, three patients were diagnosed as having obstructive sleep apnea (OSA) and PLMS, five as having PLMS only, and one had no sleep disorder. There were three clinical parameters of interleukin-6 (IL-6), C-reactive protein (CRP), and ferritin which had significant correlation ($p < 0.05$, Spearman`s correlation test) with some objective sleep parameters in the NPSG. IL-6 showed a positive correlation with limb movement arousal index (LMAI) (r=0.762), and a negative correlation with slow wave sleep percent (SWS%) (r=-0.762). CRP was also positively correlated with limb movement index (LMI) (r=0.700). Ferritin was positively correlated with the lowest oxygen saturation (r=0.743), and negatively correlated with oxygen desaturation index (desaturation more than 10%) and relative snoring time (%) (r=-0.903 and -0.850 respectively).
Conclusion: This study showed that increased CRP is associated with the decreased amount of SWS in HD patients with EDS. Particularly, the increment of CRP and IL-6, inflammatory markers in CRF, were shown to be associated with greater severity of PLMS. These suggest that chronic inflammatory activity of CRF could affect the severity of PLMS and/or impaired sleep architectures. Our results also showed the relative deficit of iron in HD patients was associated with the severity of sleep breathing disorder (SBD). Further studies on the relationship of CRP and IL-6 with PLMS and that of ferritin with SBD in CRF patients remain to be done to clarify how the pathophysiology of CRF is related with the sleep architecture or sleep disorders in HD patients.

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Heart Rate Variability During Sleep in Women With Fibromyalgia

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Introduction: Fibromyalgia (FM) is a disabling, chronic, pain disorder that affects 2-4 % of the general population and predominantly affects women. Insomnia is common in FM and may be associated with dysregulated autonomic nervous system (ANS) functioning during sleep. The purpose of this study was to compare patterns of heart rate variability (HRV), a measure of ANS balance/imbalance, in women with FM (n = 29, mean age 45 ± 8.2 years) and controls (n = 21, mean age 42.4 ± 7.4 years).
Methods: A comparative secondary analysis was performed on data obtained from a previous study of FM conducted at a university-based sleep research laboratory. Subjects who met standard criteria for FM were recruited from a tertiary clinic devoted to the evaluation of chronic fatigue. Women with self-reported good sleep were recruited from the community. Women completed 2 consecutive nights of polysomnographic (PSG) assessment and the Diagnostic Interview Schedule (DIS). Time and frequency domain HRV measures for total sleep time, non-rapid-eye-movement (NREM), and REM sleep states were compared for these two groups, based on the second night of PSG heart signal and sleep data.
Results: Women with FM exhibited significant sleep disturbance compared to controls (Mann-Whitney Test, SINDX: FM = 0.79 ± 0.10, C = 0.92 ± 0.03, $p < .001$; Total Sleep Time (min): FM 374 ± 67, C = 418 ± 34, p = .023; NREM Sleep Stages 1,2,3,4 Combined (%): FM = 66.3 ± 8.2, C = 71.9 ± 4.2, p = .003; and REM Sleep Stage (%): FM = 17.1 ± 4.9, C = 21.7 ± 5.2, p = .002). However, General Linear Model analyses (% sleep stage, age, body mass index, DIS), showed no significant differences in HRV measures between these two groups for Total Sleep Time Mean RR (ms) (FM = 885 ± 117, C = 944 ± 114, p = .446), SDNN(sqrt) (FM = 9.05 ± 1.24, C = 8.76 ± 1.27, p = .475), LF(log) (FM = 2.57 ± 0.31, C = 2.60 ± 0.31, p = .872), HF(log) (FM = 2.27 ± 0.49, C = 2.34 ± 0.38, p = .750), NREM Sleep (stages 2, 3, 4) (Mean RR (ms) (FM = 903 ± 126, C = 961 ± 121, p = .115), SDNN(sqrt) (FM = 8.09 ± 1.09, C = 7.86 ± 1.21, p = .897), LF(log) (FM = 2.36 ± 0.33, C = 2.44 ± 0.35, p = .335), HF(log) (FM = 2.25 ± 0.52, C = 2.38 ± 0.42, p = .404), or REM Sleep (Mean RR (ms) (FM = 881 ± 119, C = 923 ± 110, p = .421), SDNN(sqrt) (FM = 8.48 ± 1.59, C = 8.16 ± 1.20, p = .569), LF(log) (FM = 2.42 ± 0.42, C = 2.58 ± 0.33, p = .261), HF(log) (FM = 1.98 ± 0.63, C = 2.14 ± 0.42, p = .550).
Conclusion: These findings show that despite significant sleep disturbance in FM, there was no evidence of ANS dysregulation during sleep as measured by heart rate variability.

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Ronchopathy and Chronic Mountain Sickness. A Case Control Study

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Introduction: Chronic Mountain Sickness, Monge`s disease, (CMS), is a condition described in high altitude natives who lose abilities to cope with their enviroment. Several physiological modifications have been observed, bone marrow hyperplasia, increased hematocrite, high levels of erythropoietin that reflect compensatory changes to hypoxemia. In the same way some cardiorespiratory special features have also been observed, periodic breathing pattern, carotideal sinus hyperthrophy, positive correlation between high hematocrite and diastolic high blood pressure and increased pulmonary artery pressure. In the andean natives, genetically modifications has not been found as has been proposed in some sherpas populations. Therefore in the andeans the process is aclimatation and is not a real adaptation. Excessive hematocrite has been found in 33% of middle age population from some peruvian high altitude areas. Age and lower chronic respiratory diseases have been proposed as risk factors for CMS. There is an overlap between CMS symptoms and sleep respiratory breathing disorders (SRBD). Although the mechanism of CMS is currently unknow some theories have considered the role of sleep in the origin of this condition.Therefore we looked for symptoms of some common sleep disorders in a group of CMS patients and controls from native highlanders in Cerro de Pasco city, which is located at 4338 meters of altitude in the peruvian Andes.
Methods: This was a paired transversal case-control study between groups matched by age. Inclussion criteria: males, age between 40-60 yo, natives permanent residents in Cerro de Pasco (at least ten years) without trips to localities below 2500 meters of altitude for periods above 3 months in the last year. Exclussion criteria: miners, smoking history, asthma, previous cardiac or pulmonary disease and no therapeutic bleeding in the last three months. Cases were defined by CMS symptoms and hematocrite above 64%. Controls were healthy neighbours. Both groups complied inclussion and exclussion criteria. The information was obtained by a 34 items quality of sleep self-administrated questionary (QSQ), Snore/ hypersomnia scale, Epworth Sleepiness scale, CMS number of symptoms , measures of hematocrite, height, weight and neck perimeter.Body mass index(BMI) was calculated. The statistics were done with EpiInfo 2000 software to obtain averages and p values with Fisher`s test.p<0.05 was considered significative.
Results: There were 15 controls and 14 cases with an average age of 43 and 45 yo respectively (p=0.5). Hematocrites were 54% and 68% (p=0.0002). Epworth scale score's means were 8.3 and 11.4(p=0.05),Snore/hypersomnia scale scores were 6.27 and 12.67 (p=0.019),number of positive answers to QSQ were 6.6 and 14.08 (p=0.04), neck perimeter means were 37.8 cm and 39.42 cm (p=0.21),and BMI means were 26.21 and 26.1 (p=0.92). Headaches, morning headaches and hypnagogic allucinations were more frecuently mentioned in the CMS group. Symptoms related to Gastroesophagic Reflux (GER) as weekly antiacid use to relief stomachal complaints and epigastric matutine burning, chronic cough, matutine hoarseness and waken up with cough and wheezing in the middle of the nigth had p values <0.05 as well as grouped symptoms for obstructive sleep apnea (heavy snoring, witnessed apneas, high blood pressure, personality changes, weight gain, nocturnal sweating and irregular heart beats).
Conclusion: In a group of paired CMS case-control matched by age we found more ronchopathy, and more symptoms of sleep apnea and GER. These findings deserve more attention on the possible role of obstructive sleep apnea or upper airway ressistance syndrome and GER in CMS.

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Daytime Activity/Nap Patterns and their Relationship to Fatigue during Adjuvant Chemotherapy for Breast Cancer

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Introduction: Introduction: In recent years, a strong inverse relationship has been reported between daytime activity and fatigue levels in women receiving adjuvant breast cancer chemotherapy. Yet, little is known about the role of daytime naps on daytime activity in modifying cancer-related fatigue. One study recommended that patients undergoing radiation therapy increase their night's sleep to compensate for the increased time awake after sleep onset (WASO). The role of daytime activity/naps needs to be clarified in relationship to fatigue because women commonly take long daytime naps to compensate for prolonged WASO time. The purpose of this study is to describe the relationships between daytime activity/nap patterns and cancer-related fatigue during adjuvant chemotherapy for breast cancer. It is hypothesized that short naps may be restorative, but that long naps may interfere with nighttime sleep and disrupt circadian rhythms.
Methods: Methods: Prospective, repeated measures, feasibility design; enrolled 25 Caucasian post-op women with Stage I or II breast cancer, receiving four cycles of out-patient Adriamycin-based chemotherapy. Mean age 54.3, most were married, employed full or part time, with some college education. Instrumentation included the Morin Sleep Diary and Piper Fatigue Scale. Wrist actigraphy (Ambulatory Monitoring, Inc.) documented 24 hour sleep/wake patterns for 7 days after each chemotherapy treatment. All women received a 4 component behavioral sleep intervention, with instructions to limit daytime naps. SPSS was used to test relationships among variables.
Results: Results: The pattern of daily naps during the first week after the first 2 chemotherapy treatments followed a bell curve, ranging from 14% of Day 1 to a peak of 25% of Day 3, then back to 10% on Day 7 per actigraph. Mean daily minutes spent napping during the first 4 days after the treatment ranged from a first treatment high of 48.7 (0-135) to a fourth treatment low of 31.6 (0-131) per sleep diary. Mean daily minutes spent napping for days 5-7 post-treatment ranged from a high at the first treatment of 40.6 (0-180) to a low of 17.6 (0-60) minutes per sleep diary. Mean sleep efficiency ranged from 85% to 89%. No significant correlation was found between total nap time and fatigue. There were no significant differences in fatigue levels or WASO when comparing shorter versus longer nap duration. Higher daily activity per actigraph was correlated with lower fatigue at treatments 3 & 4 (r=-.48-.58, p<.0.01-.03). Higher mean daily awakenings per actigraph were significantly correlated with higher fatigue at treatments 3 & 4 (r=.47-.62, p<0.04-.005).
Conclusion: Conclusion: Patterns of napping followed a bell curve during the first week after chemotherapy. Total daily nap time varied widely, but means remained within the desired range when receiving the behavioral intervention. In this small sample, nap duration was not correlated with fatigue or WASO. The negative correlation between activity and fatigue was supported at the later treatments. These findings can be used for comparison with findings from larger studies aimed at reducing cancer-related fatigue and maintaining chronologic rhythms during chemotherapy treatments.

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The Pattern Of Sleep, Fatigue, Mood And Quality Of Life During Chemotherapy

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Introduction: Fatigue is the single largest complaint of cancer patients, yet little research has examined the relationship between fatigue and sleep. Fatigue is likely caused by multiple factors including physiological factors (e.g., pain, anemia), psychological factors (e.g. depression, anxiety), socio-cultural factors (e.g., education) and chronobiological factors (e.g. sleep and circadian rhythms). In an attempt to better understand the relationship between fatigue and sleep, women with newly diagnosed breast cancer had their sleep recorded with actigraphy, completed questionnaires on sleep, fatigue, quality of life, depression and menopausal symptoms.

Methods: Data are presented from 65 women with a mean age of 51.7 years (SD 10.4; range 34-79). All women had been diagnosed with Stage 1 (26%), stage II (44%), stage III (19%) or stage IIIA (11%) breast cancer and were scheduled to begin adjuvant or neoadjuvant anthracycline-based chemotherapy. Data were collected pre-chemotherapy (week 0) and during the three weeks of cycle 1 chemotherapy (C1W1 = chemotherapy administration; C1W2 = point of nadir of blood counts; C1W3 = recovery). During each week of data collection, an actigraph (Actillume II, Ambulatory Monitoring, Inc) was worn for three consecutive 24-hour periods, and questionnaires on depression (CES-D), fatigue (MFSI) quality of life as affected by breast cancer (Fact-B), quality of life as affected by sleep (FOSQ) and reported sleep quality and quantity (PSQI) were completed. SAS was used to examine the quadratic pattern over the four weeks.

Results: For the objective sleep findings, sleep was worse during C1W1 compared to baseline and to C1W2 and C1W3 (all at $p<0.05$). Total naptime was 1.89 hours (SD 1.6) during C1W1 vs. 1.1 hours (SD 1.0) during week 0, C1W2 and C1W3, while total sleep time was 6.4 hours (SD 2.2) during C1W1 vs. 5.9 hours (SD1.7) week 0, C1W2 and C1W3. For the subjective reports, mood, fatigue, sleep and quality of life were worse during all three weeks of treatment compared to baseline and were all equally bad during C1W1, C1W2 and C1W3 (all $p<0.05$).

Conclusion: The pattern for the objective measures of sleep suggested that the amount of sleep both during the day and night was increased during the week of chemotherapy (cycle 1 week 1) compared to baseline and the two weeks following chemotherapy administration. On the other hand, the subjective reports of sleep, mood, fatigue and quality of life suggested decrements throughout the three weeks of cycle 1 compared to baseline. In other words, there was a tendency for the objective sleep measures to show rapid rebound while the subjective measures showed a slow rebound. We continue to examine these patterns to better understand the relationship between the complaint of fatigue and other possible confounds such as sleep and circadian rhythms.

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Sleep Efficiency; Effect Of Proton Pump Inhibitor Therapy In Patients With Marked Sleep Disturbance

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Introduction: PPI therapy has been shown to reduce esophageal acid exposure related sleep arousals and awakenings. The effect of PPI therapy on sleep quality has not been assessed. The aim was to employ objective measures of sleep efficiency in six patients with impaired sleep quality and increased esophageal acid exposure.

Methods: Six patients who had esophageal reflux events by pH study and whose sleep efficiency was < 80% were included. The protocol involved two nocturnal polysomnographic recordings in the Jefferson Sleep Disorders Center laboratory with simultaneous esophageal pH monitoring. After the first overnight stay, patients were given omeprazole 20 mg to take twice daily for two weeks. A decrease in the esophageal pH below 4.0 was considered a reflux event. An arousal was defined as an abrupt frequency increase on EEG (except spindles), or wakefulness, lasting for at least 3 seconds but less than 15 seconds. An awakening was defined as a period of scored wakefulness lasting for at least 15 seconds. Reflux events were associated with awakenings or arousals if they occurred within five minutes prior to these events. Sleep efficiency is the ratio of total sleep time to time spent in bed, expressed as percentage. Sleep efficiency less than 80% was considered to be abnormal. Total awake time is the cumulative amount of time spent awake during the recording.

Results: Six subjects were studied. (4 men and 2 women; age range 33-62 years; mean 41.3 years). Body mass index was 27.2 2.2. Data were analyzed pre and post treatment with omeprazole. Total sleep time (mean SE) increased from 294.0 15.9 minutes to 345.6 55.6 minutes ($P < 0.05$). Total wake time decreased from 99.1 17.9 minutes to 46.1 15.3 minutes ($P < 0.05$). Sleep efficiency increased from 70.2% to 81.6% ($P < 0.05$). REM sleep time improved from 55.0 4.5 minutes to 94.5 18.9 minutes ($P < 0.05$). Number of awakenings decreased from 8.7 2.0 to 3.2 0.7 ($P < 0.01$). Changes in other variables such as time in stages 1,2, and delta (3 and 4), sleep latency and degree of daytime refreshment were not significant ($P > 0.05$). The number of reflux events associated with arousals decreased from 3.3 1.2 to 1.5 0.6 ($P < 0.05$). The total time spent at pH < 4 decreased from 59.2 13.7 to 4.0 1.6 ($P < 0.05$).

Conclusion: These preliminary findings suggest that, in patients with disturbed sleep and gastroesophageal reflux, sleep parameters improve after treatment with effective antisecretory therapy.

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Ambient Illumination And Melatonin: Contribution Of Ophthalmic Diseases

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Introduction: Light influences numerous biological rhythms and behavioral markers. In the laboratory, differing experimental paradigms have demonstrated light's entraining effects. In the natural environment, ambient illumination influences sleep/wake cycles and mood. Recently,

we reported data that eye diseases mediated the relationship of low ambient illumination to depressed moods. In the present study, we tested the hypothesis that eye diseases have a similar influence on the relations between ambient illumination and the circadian rhythm of melatonin.

Methods: The sample comprised Black (46%) and White (54%) Americans (n = 59, mean age: 69 ± 7 years) of both genders (women: 82% and men: 18%). Individuals provided demographic and health-related data. Those meeting eligibility criteria underwent eye exams at SUNY Downstate to obtain visual acuity, visual field defects, intraocular pressure, cup-to-disk ratio, and nerve-fiber-layer thickness. During the week following eye exams, participants wore an actigraph (Actiwatch-L) monitoring 24-hr ambient illumination. Fractional urine samples for aMT6s were obtained in the last 24 hours of the recording. Samples were retrieved and sent to UCSD where they were assayed using Bhhlmann Labs, 96 well ELISA kits (ALPCO). Cosine analyses were performed on illumination and aMT6s data, yielding illumination and melatonin mesors and acrophases. All distributions were examined for normality and were transformed where appropriate. Some of the volunteers (n = 22) provided insufficient samples for accurate estimation of aMT6s acrophases, thus were excluded from analyses.

Results: Most volunteers (78%) were in good health, but 27% were visually impaired according to standard criteria. Median illumination and aMT6s excretions were 635lux and 286ng/h, respectively, and the median for acrophases of illumination and aMT6s were 14.21 hours and 3.36 hours, respectively. To examine which factors were predictive of aMT6s mesors and acrophases, we employed two hierarchical regression models. The first uses aMT6s mesors as the dependent variable and four compound independent factors (i.e., illumination, demographic, medical, and eye) entered in a stepwise manner. The illumination factor accounted for 14% of the variance in aMT6s mesors. The variance accounted for by demographic, medical, and eye parameters were 11%, 11%, and 30%, respectively; overall, the model accounted for 66% of the variance. The most significant factors in this model were: illumination acrophases (rp = -0.35) and cup-to-disk ratios: vertical (rp = 0.63) and horizontal (rp = -0.64). In the second model, where aMT6s acrophases was the criterion, illumination accounted for 1% of the variance, followed by demographic (22%), medical (4%), and eye (8%). Altogether, this model accounted for 35% of the variance; the most significant factor was the volunteer's age (rp = 0.37).

Conclusion: These findings are consistent with previous reports showing associations between habitual daily illumination and melatonin rhythms. The observation of weaker relationships between the independent factors and melatonin acrophases may, in part, be attributed to the large variability in aMT6s acrophase distribution (mean = 4.65 ± 4.13). These results support the notion that healthy eyes are necessary for adequate circadian entrainment, and that human circadian rhythm studies should screen for ophthalmic dysfunctions.

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Excessive Daytime Sleepiness In Parkinson's Disease

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Introduction: The objective of our study was to evaluate the daytime sleepiness (DS) in a group of patients with Parkinson's Disease (PD) and compare it with a control group without PD.

Methods: Thirty four patients with PD and thirty seven non-PD controls were studied. Diagnosis of DS was performed by the Epworth Sleepiness Scale (ESS) in three versions according Hobson DE et al . All the patients answered the three ESS versions. The PD group was compared with the control group.We applied Chi-Square Test to the data.

Results: The mean age of the patients was 59.97±12.56 years in the control group and 61.34±8.68 in the PD group. The mean value of ESS version 1 (classic model) was 7.46±4.34 in the control group and 10.74±6.00 in the PD group. These results showed significant difference (p:0.009). With ESS version 2 we found means of 2.68±3.6 in the control group and 5.69±5.13 in the PD group. There was significance with p:0.005. The ESS version 3 showed tendency to daytime sleepiness in PD group, but statistical analisys could not be done (Kurtose of 6.336 and 15.360).

Conclusion: Our data indicate association of daytime somnolence and PD when compared with a similar group without PD. Excessive daytime sleepiness is a common and potentially injurious condition related to PD that should be considered part of the clinical spectrum of the disease.

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Disordered Sleep, Sleepiness and Depression in Chronically Tired Patients with Systemic Lupus Erythematosis (SLE)

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Introduction: Persistent tiredness in patients with Systemic Lupus Erythematosis (SLE) is common and distressing but poorly understood. It is unclear whether these patients are suffering from physical fatigue, depression, or excessive daytime sleepiness associated with disordered sleep. In this study we conducted a systematic chart review with the aim of describing the sleep physiology of tired SLE patients and exploring the causes of this tiredness. We hypothesized that depression and primary disordered sleep with sleepiness could be differentiated as causes of tiredness in this population.

Methods: The sample consisted of 37 SLE patients (33 women and 4 men; mean age 44 yrs ± 11) who had been referred to the sleep clinic for the investigation of overwhelming tiredness. All patients fulfilled the ACR criteria for the classification of SLE and were assessed for fibromyalgia and disease activity (SLEDAI) at the lupus clinic. At the sleep clinic, the subjects were evaluated with standardized ratings for sleepiness (Epworth Sleepiness Scale; ESS) and depression (Beck Depression Inventory; BDI), and with overnight polysomnography followed by daytime multiple sleep latency tests (MSLT).

Results: Disordered sleep physiology was common in SLE patients. Polysomnography showed numerous nocturnal awakenings (mean 24.7± 12.6) and impaired sleep efficiency (mean 75.1± 19.1%). A high level (>40%) of alpha EEG Non Rapid Eye Movement sleep activity was seen in 78% of patients. Primary sleep disorders were diagnosed in 46% of patients, comprising 9 patients with periodic limb movement disorder (mean PLM index 30.0± 12.7), 10 patients with obstructive sleep apnea (mean RDI 19.3± 10.3), and one patient with narcolepsy including cataplexy. Remarkably, 51% of the patients were pathologically sleepy on both the ESS and MSLT (mean sleep latency < 10 minutes). This excessive daytime sleepiness was not related to sleep restriction or the presence of primary sleep disorders other than narcolepsy. Moreover, there was no association between pathological sleepiness and SLE disease features such as neuropsychiatric SLE, medications, comorbid fibromyalgia, or indices of SLE disease activity. As a whole, the study group reported moderate depression (mean BDI = 15.9± 9.6). Within the group, the sleepy patients had significantly lower BDI scores than the non-sleepy patients (11.7± 7.2 vs. 20.4± 9.9, p<0.02), and fewer of the sleepy patients were depressed (BDI>18; 14.2% vs. 57.1%, p<0.02).

Conclusion: Primary sleep disorders, sleepiness and depression are

common in tired SLE patients. Tiredness in SLE that is the result of excessive daytime sleepiness can be distinguished from tiredness of depression. Such distinctions may be used to identify the most appropriate treatment for tired SLE patients.

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Effects Of Sport-Related Concussion On Sleep

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Introduction: More than 300 000 concussions occurring in sports are indexed each year in the United States. This incidence is certainly underestimated since only a small percentage of the concussions are reported. The post-concussion syndrome is generally characterized by headaches, memory problems, fatigue, difficulty concentrating, dizziness and sleep disorders. A few studies investigated subjective sleep complaints of concussed subjects and found difficulties in maintaining sleep, increased sleep latency and unrecuperative sleep with the complaint of feeling tired upon awakening in the morning. The aim of the present study was to investigate the effects of sport-related concussion on sleep architecture.
Methods: Five athletes who sustained a concussion in hockey or football (age: 25.8 (6.4) years, 4 men) and ten age-matched normal controls (age: 25.0 (5.0) years, 8 men) entered the study. All subjects were recorded for two nights in the sleep laboratory. Athletes had a past history of 4.4 (1.8) diagnosed concussions. The mean time elapsed since their last concussion was 18.8 weeks. All concussed athletes fulfilled a symptom questionnaire. They all complained of drowsiness, three athletes reported hypersomnia i.e. difficulty to stay awake during the daytime and two presented insomnia. No subject showed a PLMS index greater than 10 and none of the subjects had an index of respiratory events (apneas and hypopneas) greater than 5 per hour of sleep. Group differences in polysomnographic data for the second night were assessed with Student t-test.
Results: Concussed athletes showed a reduction in the percentage of slow wave sleep (SWS) in comparison with control subjects (concussion group: 5.04 (4.0)%, control group: 14.43 (7.61)%, $p = 0.02$). Concussed group also showed an increase in percentage of stage 2 sleep (concussion group: 66.5 (5.7)%, control group: 57.6 (7.7)%, $p = 0.04$). No between-group difference was observed for REM sleep, sleep latency, total sleep time, number of awakenings, sleep efficiency and microarousal index.
Conclusion: Results of the present study showed an important and specific reduction in SWS following sport-related concussions. This reduction in SWS is somewhat surprising since the polysomnographic recording was done more than four months after the last concussion. The long-term deprivation of SWS may be responsible for the complaint of unrestorative sleep and daytime fatigue and sleepiness, but may also contribute to the cognitive deficits generally observed in concussed athletes.

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Sleep Quality, Daytime Fatigue and Sleepiness in Patients with Heart Failure

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Introduction: Sleep quality has important implications on daytime functionality. While it is commonly stated that patients with heart failure (HF) frequently suffer from daytime fatigue, sleep quality and daytime fatigue in patients with HF has not been evaluated. Objective: To examine sleep quality, daytime sleepiness and daytime fatigue in patients with stable HF.
Methods: HF was defined as a clinical diagnosis of HF with an LV ejection fraction <45%. Sleep disordered breathing (SDB) was defined as a respiratory disturbance index (RDI) > 15. All subjects underwent overnight polysomnography (PSG) and questionnaire evaluation including Pittsburgh Subjective Sleep Quality Index (PSQI) measuring the subjective quality of sleep, Fatigue severity scale (FSS) measuring the daytime fatigue, Functional Outcome of Sleep Questionnaire (FOSQ) measuring functional status outcome and Epworth Sleepiness Score (ESS) measuring subjective daytime sleepiness. PSQI was used to evaluate subjective quality of sleep, FSS was used to evaluate day time fatigue, FOSQ was used to measure functional status outcomes, and ESS was used to evaluate subjective daytime sleepiness. Objective quality of sleep was determined
Results: Sixteen subjects completed the study protocol. Twelve had sleep disordered breathing, whereas 4 did not. Subjects in both groups had poor subjective sleep quality (PSQI-global mean score 8 and 10.25+- in SDB and non-SDB group respectively) daytime fatigue (FSS >35) but without subjective daytime sleepiness (ESS <10). There were no differences between the subjects with and without SDB in age, sex, ejection fraction, body mass indices, PMLS, ESS, FSS, FOSQ global index, sleep efficiency, total sleep time and sleep latency as measured by PSG.
Conclusion: Stable HF patients tended to have poor sleep quality regardless of whether or not they have SDB. Furthermore, daytime fatigue without sleepiness is common in stable HF patients regardless of SDB.

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Relationships Between Pain and Sleep Disturbances Depending Caffeine Use in Persons with Rheumatoid Arthritis Taking Methotrexate

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Introduction: Rheumatoid arthritis (RA) is commonly treated with methotrexate (MTX), which increases levels of adenosine, an endogenous anti-inflammatory. Recent studies demonstrated that caffeine, an adenosine antagonist, reduced the disease-modifying effects of MTX. The current study aimed to explore pain and sleep disturbance depending on MTX use and to explore the effect of caffeine use on the relationships between pain and sleep in persons using MTX.
Methods: Data were pooled from three studies of symptoms in women with RA. Consumption of caffeinated products was assessed at baseline and converted to milligrams of caffeine. Pain was assessed every evening using an 11-point numerical rating scale. Sleep quality was assessed on a five-point Likert-type scale, and subjective sleep latency was estimated by participants. Objective sleep outcomes were measured

by wrist actigraphy. Pain and sleep measures were averaged over 2 to 3 nights. Premenopausal women were assessed in the early follicular phase of the menstrual cycle to control for the effects of hormonal variation. T-tests, or Kruskal-Wallis tests on skewed variables, were performed to compare symptoms in women taking MTX and those not taking MTX. The group taking MTX was divided into low and high caffeine consumers based on a median split of daily caffeine intake (0-99 mg, 100-340 mg). Pearson's correlations between pain and sleep disturbances were performed to explore relationships between these symptoms in persons taking MTX who have low and high caffeine consumption. Given that this was an exploratory analysis, a comparison type I error rate of 0.05 was used.
Results: The sample included 33 women with a mean age of 46.4 ± 16.0. Although average pain was 1.44 points lower in the group taking MTX (p=.020), these women experienced lower sleep efficiency (p=.012); more time spent awake (p=.005); longer objective and subjective sleep latency (p=.034, .007 respectively); and more awakenings (p=.044). Several sleep outcomes that were not correlated with pain in low caffeine consumers were strongly correlated in high caffeine consumers, including subjective sleep latency (low/high respectively) r=.015, r=.475; minutes spent awake r=.141, r=.696; and sleep efficiency r=-.074, r=-.690. In both the low and high caffeine groups, pain was correlated with subjective sleep quality (respectively, r=-.528; r=-.629) and number of wake episodes (r=.638; r=.755), but the correlations were stronger and significant in the high caffeine group.
Conclusion: Women using MTX experienced less pain but greater sleep disturbance than those not taking MTX. Pain may have been attenuated by disease-modifying effects MTX. It is unclear why these women experienced more sleep disturbances, given that MTX raises adenosine levels, which should facilitate sleep. Worse disease status warranting use of MTX over milder medications may account for these findings. In those on MTX, relationships between pain and sleep disturbances were stronger in the high caffeine consumers than the low caffeine consumers. Thus, further investigation of the effects of adenosine modifiers and RA symptoms is warranted.

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Chronic, but not Acute, Nighttime Melatonin Administration Improves Sleep Quality in Hypertensive Patients

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Introduction: Properly timed melatonin administration has two distinct effects on human physiology: daytime melatonin administration can acutely induce sleep and repeated nightly melatonin can entrain the circadian sleep-wake rhythm. Patients with essential hypertension have been reported to have sleep disturbances and have recently been demonstrated to have disturbed circadian pacemaker function. Our objective was to determine whether melatonin administration might improve sleep quality in patients with essential hypertension, either by a single nighttime administration or by repeated nighttime administration.
Methods: We conducted a randomized, double-blind, placebo-controlled, crossover trial in sixteen men with untreated essential hypertension. The influence of acute (single) and repeated (3 weeks nightly) oral melatonin (2.5 mg) administration 1 hour before sleep on actigraphic estimates of nighttime sleep quality was assessed. During the recording nights at home, the subjects reported sleep details in a sleep-wake diary and wore an Actiwatch (Cambridge Neurotechnology Ltd, Cambridge, UK), on the non-dominant wrist to assess motor activity at 1 min intervals for the estimation of sleep quality. Sleep was defined by an automated algorithmic analysis of the actigraphic data between bed time and get up time derived from the sleep-wake diaries. Sleep latency was the calculated time between bed time and objectively estimated sleep onset. The percentage of time asleep while in bed was defined as sleep efficiency.
Results: Repeated melatonin administration, as compared to repeated placebo administration, increased sleep efficiency from 80% to 85% (p=0.017; 2-tailed paired student t-test) and increased estimated sleep duration from 5.6 hours to 6.1 hours (p=0.013). Sleep onset latency decreased from 33 to 22 minutes (p=0.036). Acute melatonin application had no significant effect on any of these sleep measures.
Conclusion: Regular soporific agents (e.g., benzodiazepines) improve sleep quality immediately in the first night after taking the drug. With repeated use the efficacy of those substances may decrease. These dissimilarities between the time-course of action of these substances in comparison to melatonin, suggest that the improvement of sleep by nighttime melatonin application is mediated by a different mechanism than that of regularly used sleep-promoting substances. Since melatonin is effective after repeated use, it may be especially suitable in the treatment of chronic insomnia.

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Sleep Duration and Quality in Chronic Pain Patients in Comparison to the Sleep of Fibromyalgia, Insomnia, RLS and Control Subjects

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Introduction: Chronic pain is reported by 11% of the general population and approximately 2/3 of these patients complain of poor sleep and/or unrefreshing sensation upon awakening in the morning. The aim of this retrospective analysis was to identify sleep variables that discriminate pain patients from patients with other sleep disorders (insomnia, Restless Legs Syndrome / Periodic Limb Movements during Sleep: RLS/PLMS and fibromyalgia) and from normal sleepers.
Methods: The data of 10 subjects in each group were retrieved from the sleep laboratory data bank. Patients in each group were matched for age (mean ± SE; 55 ± 3yrs) and gender (5 female and 5 male). Polysomnographic recordings included electroencephalogram, electrooculogram, electromyogram and respiratory variables. Sleep stages, PLMS, sleep apneas and micro-arousals were scored according to standard criteria. Sleep apnea index was assessed for 86 percent of the subjects, and the overall result was 0.9 ± 0.2 and the range was from 0 to 6.1. All insomnia patients were diagnosed with psychophysical insomnia. As confirmed by clinical interview, pain patients had a history of chronic shoulder, lower back, leg or abdominal pains.
Results: Comparisons were done for sleep duration, sleep efficiency, sleep latency, REM latency, awakenings/hr, micro-arousals/hr, sleep stage shift/hr, percentage of stage 1, stage 2, stages 3+4 and REM sleep, PLMS index, sleep hypopnea index and sleep apnea index. Of these variables, only sleep duration, sleep efficiency and PLMS index showed a significant group effect (ANOVA: p<0.01). The sleep duration of chronic pain patients was significantly shorter than that of controls (343.3 ±

23.6min vs. 436.1 ± 10.4 min respectively, p<0.01). Furthermore, the sleep efficiency of chronic pain patients was also significantly lower than that of RLS patients (76.1 ± 4.0% vs. 88.1 ± 1.6% respectively, p<0.05) and of controls (76.1 ± 4.0% vs. 91.3 ± 1.4% respectively, p<0.01). Insomniac and fibromyalgiac patients had intermediate values for sleep duration and sleep efficiency, but these were not significantly different from controls. The PLMS index of RLS patients was significant higher in comparison to that of other groups (RLS: 33.4 ± 3.4 vs. fibromyalgia: 11.0 ± 6.6, p<0.05; vs. chronic pain 10.2 ± 3.2, p<0.05; vs. insomnia 1.7 ± 0.8, p<0.001; vs. controls 1.7 ± 0.9, p<0.001). In chronic pain patients, the PLMS index was also higher than that of insomniac patients and controls (10.2 ± 3.2 vs. 1.7 ± 0.8, 1.7 ± 0.9 respectively, p<0.05). There was no correlation between PLMS and sleep efficiency in any group at the exception of insomnia patients (R=0.64, p=0.05), and no correlation between PLMS and sleep duration in any group.
Conclusion: This study supports the complaint of chronic pain patients about having poor sleep quality in comparison to controls since their sleep duration and sleep efficiency were lower. On the other hand, the PLMS index was higher in RLS, chronic pain and fibromyalgia patients than in controls. The presence of PLMS in chronic pain patients might influence sleep quality more importantly than originally thought.

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Effects of Smoking and Smoking Cessation on Sleep Niggemyer KA, Koru-Sengul T, Houck P, Shiffman S, Buysse DJ University of Pittsburgh School of Medicine

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Introduction: Both smoking and smoking cessation have deleterious effects on sleep. Smokers are significantly more likely than nonsmokers to report insomnia and daytime sleepiness. Similarly, smoking cessation has been associated with further sleep disruption. Most current data regarding the adverse effects of smoking on sleep are derived from survey data collected at single time points. The aim of this study was to analyze longitudinal subjective sleep data from daily sleep diaries during two-weeks of baseline cigarette smoking and a subsequent four-week period of smoking cessation without nicotine replacement therapy.
Methods: Subjects included 271 adults (mean 44yrs) who were smoking greater than 10 cigarettes per day (mean 22 cigarettes/d), and who enrolled in a behaviorally-oriented smoking cessation program. Subjective sleep variables were recorded in a daily electronic diary completed at waking over a two-week baseline period and a four-week cessation period (11,514 person-days and 105,559 cigarettes recorded). Sleep variables included sleep duration and four qualitative questions (4-point scales): Trouble falling asleep?, Do you feel rested?, Number of awakenings?, Rate how well you slept. Sleep quality was quantified as the mean of these four sleep items. Analyses focused on differences in mean scores between smoking baseline and intervals before the quit date, before lapses (any occasion of smoking), and before relapses (sustained smoking). Survival analysis was used to examine the relationship between baseline variables and time of lapse/relapse.
Results: At the designated quit date, 184 of 271 subjects (68%) successfully quit smoking (abstinent for 24 hrs). Of these, 32 relapsed (18%), 84 lapsed (45%), and 68 remained abstinent for 21 days (37%). For the sample as a whole, sleep quality (p<0.006) and sleep duration (p<0.003) worsened from baseline (day -14 to -3) to pre-cessation (day -3 to 0). Survival analyses showed no relationship between time to lapse or relapse and baseline sleep quality or sleep duration, pre-cessation sleep quality or sleep duration, or baseline number of cigarettes smoked. However, in the three days preceding lapses, mean sleep quality was worse and sleep duration greater (p<0.005 and p<0.04 respectively) when compared to baseline.
Conclusion: This longitudinal study showed that sleep quality and duration significantly worsened in the three days prior to the quit date relative to baseline. This "anticipatory effect" has not been described previously. Baseline sleep quality, sleep duration, and quantity of smoking were not associated with time to lapse or relapse, but lapses were preceded by worsening sleep quality and increased sleep duration. Incorporating measures to improve sleep quality may be of benefit in smoking cessation programs with a particular focus on sleep just before quitting. Worsening sleep quality and increasing sleep duration relative to baseline may signify impending episodes of lapses in smoking cessation.

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Nocturnal Oxygen Desaturation in Pulmonary Arterial Hypertension

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Introduction: Nocturnal oxygen desaturation (NOD) not related to sleep-disordered breathing has been reported in patients with primary pulmonary hypertension (PPH). Untreated NOD may worsen the pulmonary hypertension having deleterious effects in these patients. We describe the incidence of NOD in a group of patients with pulmonary arterial hypertension (PAH), and evaluate associated factors.
Methods: A prospective study of 24 patients with PAH who underwent overnight oximetry. Patients who spent more than 10% of the total sleep time with a saturation of oxygen (SpO2) <90% were considered "nocturnal desaturators". Variables analyzed included: demographics, pulmonary function tests, pulmonary artery pressures, right ventricular systolic pressures, hemoglobin levels, and 6-minute walk test. Student's t-test was used to compare variables between non-desaturators and desaturators.
Results: Of the 24 patients (20 female/4 male; mean age: 49.3 +/- 13.9 years), 12 (50%) were nocturnal desaturators. PPH was the diagnosis in 91.6% of the desaturators, and 58.3% of the non-desaturators. The comparison of the different variables (mean +/- SD) between non-desaturators and desaturators showed the following results: FEV1 (74.9 +/- 15.46% predicted vs. 75.5 +/- 13.8% predicted, respectively; p=0.46), diffusing capacity for carbon monoxide (69 +/- 29.44% predicted vs. 65.3 +/- 24.7% predicted, respectively; p=0.38), resting SpO2 (95.3 +/- 4.09% vs. 93.9 +/- 6%, respectively; p=0.25), change (decrease) in SpO2 during 6-MWT(5.83 +/- 4.9% vs. 7.66 +/- 4.4%, respectively; p=0.08), mean pulmonary artery pressure(44.49 +/- 14.26 vs. 49.55 +/- 12.39 mmHg, respectively;p=0.18), right ventricular systolic pressure (57.9 +/- 17.6 vs. 72.63 +/- 21.2 mm Hg; p=0.05),and hemoglobin level (12.71 +/- 1.73 vs. 14.27 +/- 1.75 g/dL, respectively; p=0.02).
Conclusion: A high incidence of nocturnal oxigen desaturation is seen in patients with PAH. An elevated right ventricular systolic pressure and a high hemoglobin level seem to correlate with a low SpO2 in this patient population. The inclusion of overnight oximetry in the routine work-up of patients with PAH is warranted.

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Treatment Time of Day Alters the Sleep/Wake Patterns of Patients on Chronic Hemodialysis

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Introduction: Chronic hemodialysis (HD) is typically administered three times a week at a particular time of day: early or mid morning, mid or late afternoon. Although we have previously reported on the acute effects of the dialysis treatment on sleep, whether or not treatment time of day alters sleep/wake patterns has never been examined. Thus, we studied a sample of HD patients via continuous ambulatory polysomnography (PSG) to explore relationships between selected sleep variables and the time at which they received their treatments.
Methods: The sample included 31 chronic HD patients, 16 males and 15 females, with a mean age of 51.1 + 11.0 years and who were free of other chronic conditions. Subjects underwent continuous ambulatory PSG (MR 95; Oxford Instruments) to evaluate sleep architecture and continuity for one (n = 3) to two (n = 28) 42-hour periods beginning at 6 PM the night before HD and ending at 12 PM the day following treatment. Data were pooled from the nights before HD, the days of HD, and the nights following HD (determined by lights on and off as recorded by the subjects). Treatment time of day was the mean time that HD was initiated during the recording period. Because data were not normally distributed, the Spearman rho (rs) correlation procedure was used for analyses.
Results: Treatment times of day ranged from 05:55 to 15.51 (mean = 10:15 + 3:25). Average total sleep time was 314.5 + 72.1 minutes for the night before HD, 67.1 + 54.0 minutes for the day of (including during) HD, and 354 + 80.9 minutes for the night following HD. On the night before HD, later treatment times were significantly associated with longer sleep latencies (rs = 0.318, p = 0.040), later rise times (rs = 0.686, p < 0.001), and greater percentage of wake time after sleep onset > 120 seconds (rs = 0.372, p = 0.020). During the day of HD, later treatment times were associated with less total daytime sleep (rs = - 0.465, p = 0.004) and less percentage of daytime REM sleep (rs = -0.371, p = 0.020). On the night following HD, later treatment times were associated with later bedtimes (rs = 0.304, p = 0.040), less total sleep time (rs = - 0.0320, p = 0.040), greater amounts of NREM sleep (rs = 0.560, p = 0.001), and less REM sleep (rs = - 0.560, p = 0.001).
Conclusion: These results indicate that treatment time of day differentially affects the timing and duration of the sleep period and sleep architecture the night before, the day of, and the night following treatment. In particular, those subjects dialyzing earlier in the day appear to generally have increased quantity and quality of sleep than those who dialyze later in the day. Given our recent observation that patients who dialyze early in the day survive longer than those who receive treatment later, a close examination of the role that sleep plays in determining this outcome is warranted.

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Heart Rate Variability During REM And Non REM Sleep In Patients With Neurocardiogenic Syncope

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Introduction: Syncope is usually defined as acute and transitory loss of consciousness. Electrocardiogram is usually normal and there are no evidences of structural cardiac disease. A common mechanism includes a reflex response to trigger stimulus (whatever stimuli is present). The mechanoreceptors found in the atrial and ventricular myocardium, are implicated in starting the reflex in the classical vasovagal syncope Increase in sympathetic activity leads to increased response of peripheral receptors, resulting in high catecholamine levels and paradoxical CNS response with secondary bradichardia and hypotension. Positivity of the Tilt Test ranges from 40 to 70% according to the protocol used. Autonomic impairment out of the episode has not yet been demonstrated. To analyze the sympathetic and parasympathetic components of HRV during REM and Non-REM sleep in patients with neurocardiogenic syncope compared to normal controls; in patients with positive TT compared to negative ones; in patients with positive TT with POTS compared to non-POTS responders.
Methods: Thirty seven patients diagnosed with neurocardiogenic syncope according to the International criteria, mean age (24.43 +/- 10.28), and 16 normal controls mean age (24.18 +/- 6.04), p=0.92, were selected for this study. All had normal EKG, absence of structural cardiac disease, diabetes, obesity etc, classical brief episodes, and were not using medications. Tilt table tests (TT) were performed during 45 minutes according to international protocol. TT was considered positive if it reproduces the symptoms of syncope or pre-syncope associated with hypotension and/or bradichardia. All underwent to a PSG study (Sonolab Meditron, Sao Paulo-BR) with sampling rate of 256 Hz. Heart rate variability analysis was assessed sleep during a 24-hour period by Time domain analysis, followed by FFT on 5-minute intervals during stages 3 and 4 NREM and REM sleep. Sympathetic increment index during sleep (SII), was defined according to the following formula: SII = LF Rem - LF NREM Statistics: Two-Way Anova (groups: syncope, control; and syncope TT positive, TI negative / sleep variables).
Results: Sleep parameters results: There were no significant differences found in general sleep parameters between patients and control subjects. Two subjects had no REM sleep nor stages 3 and 4 non-REM sleep. They had to be excluded of the HRV analysis. Time domain results: There were no significant differences found for all variables analyzed: Mean HR, SDNN, SDANN, RMS, PNN50 between the groups syncope vs controls and TT positive vs. negative. Frequency Domain results: It was found a significant difference in LF component of HRV during REM sleep. LF component is decreased in syncope patients compared to normals (1769.54 +/- 1738.17 +/- 3483.33 +/- 2770.84, respectively) [F(1,35)=5.3, p=0.02]. The other variables analyzed (VLF, HF, LF/HF) did not reach statistical significance during REM and non-REM sleep. There was a significant decrease in SII during REM sleep in syncope group compared to control group (-539.39 +/- 1930.78, 1314.70 +/- 2408.03, respectively) [F(1,31)=5.53, P=0.02].
Conclusion: This is the first report on HRV during sleep in neurocardiogenic syncope patients. The authors raise two main hypothesis to explain the above results: 1- there might be a sympathetic hypersensitivity during wakefulness, secondary to orthostatic stimulus, due to absence of sympathetic activation during REM sleep. 2- There might be a trend to sympathetic suppression after stimulus due to an inability of patient's CNS in increase sympathetic activity during REM sleep.

Moreover, beta-blockers are not effective in 5 out of 6 controlled studies, what reinforces this second hypothesis.

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Effects of Sleep Restriction on Slow-Wave Activity and Self-reported Pain in Patients with Fibromyalgia

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Introduction: Poor sleep is a common complaint among fibromyalgia (FMS) patients, although the putative cause of poor sleep in FMS has been debated. Delta power or slow-wave activity (SWA) in NREM sleep has been thought of as an indicator of basic sleep drive across human and animal studies. Unfortunately, there are few studies of SWA in FMS and thus it is unclear whether sleep drive is impaired in this disorder. This study investigated the distribution of SWA during baseline sleep and after 4-hour sleep delay in FMS.
Methods: Patients were screened for depression and administered the SCID depression module during their participation. No patients included here had depression. CNS-activating or sedating medications and OTC analgesics were prohibited (compliance confirmed via serum blood and urinalysis). Seven female FMS patients (mean = 45.9, range 29-63) kept a two-week-long sleep diary prior to sleeping in the lab to determine habitual bedtime. Participants then had 3 nights of PSG: lab adaptation night (8 hours), true baseline (8 hours), and sleep restriction (4 hour sleep delay). MSLTs were performed on the days following sleep study. Participants rated levels of vigor and fatigue (POMS) and pain (VAS) prior to each nap attempt. Power spectral analysis quantified SWA in consecutive NREM periods (stages 2, 3 and 4, excluding Stage 1) at baseline and following sleep delay. The ratio of SWA in the first two NREM periods was also analyzed.
Results: The ratio of SWA between the 1st and 2nd NREM period on the baseline night averaged 0.93 + 0.13 and 4/7 had a ratio < 1, indicating higher SWA power in the 2nd NREM period (normal range 1.6-2.0 as reported by Kupfer and others). Following the 4-hour sleep delay, normalization of the SWA ratio was evident in 3 of those 4 patients. For those patients with a disrupted SWA distribution at baseline, NREMPs were more consolidated and showed higher SWA in the first NREM period following the sleep delay. As expected, participants were sleepier ($t = .3.87$, $p > .01$) and tended to be more fatigued ($t = -2.48$, $p = .06$) after sleep delay. Baseline MSLTs showed hyperarousal similar to insomniacs (14.40 + 4.07 mins.) but following delay values normalized, approximating baserates of sleepiness in the general population (9.99 + 4.91 mins.). The correlation between the change in SWA ratios and pain ratings from baseline to delay trended towards significance ($r = .74$, $p > .06$), such that a normalization of the SWA distribution was strongly associated with lower self-reported pain. Finally, change in MSLT was correlated with change in self-rated pain ($r = .78$, $p = .04$).
Conclusion: This abstract includes preliminary data from a larger study involving the comparison of sleep among FMS and RA patients and normal controls. This is the first report of abnormal distribution of SWA (higher SWA in the 2nd vs. 1st NREMP) in FMS. This study also showed that abnormal SWA distribution is strongly correlated with self-reported pain, suggesting that sleep delay paradigms may be of clinical utility in FMS.

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Sleep Disturbance in Patients on Hemodialysis Versus Medically Managed Patients with Severe Chronic Kidney Disease

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Introduction: Sleep disturbances are common in patients on chronic hemodialysis (HD), an observation likely related to a variety of demographic, psychological, and metabolic factors. Although poorly appreciated, the HD treatment itself may also predispose patients to these problems via several mechanisms including intradialytic production of cytokines, inappropriately timed elevations of serum melatonin secondary to hemoconcentration, rapid fluid, electrolyte, and acid-base changes that may affect the central nervous system, and alterations in the rhythm of body temperature. An understanding of the extent to which treatment affects sleep is essential for the development of appropriate interventions designed to optimize clinical outcomes. Thus, we studied polysomnographic measures of nocturnal sleep in a sample of stable HD patients and compared results to a group of medically managed patients with advanced chronic kidney disease (CKD; Stages IV to V) not yet receiving treatment.
Methods: The sample included sixteen HD patients (8 males and 8 females; age 44.6 + 9.3 years) and 8 CKD controls (4 males and 4 females; age 43.1 + 11.8 years). Subjects were selected from those participating in a larger study and were matched on age and gender at a 2:1 ratio (HD:CKD). HD subjects received intermittent treatment three times a week; control subjects were medically managed and had an estimated creatinine clearance of 20.6 + 8.9 (range 8.2 to 31.5) cc/minute indicating advanced kidney disease. All subjects were free of other major chronic conditions. The two groups were comparable with regard to major clinical parameters including body mass index (27.0 + 5.6 vs. 25.7 + 3.2 kg/m2), blood urea nitrogen (57.9 + 18.3 vs. 58.4 + 13.4 mg%), hematocrit (35.7 + 3.4 vs. 31.4 + 4.1), and electrolytes routinely measured. Since data were not normally distributed, nonparametric procedures were used for all analyses (Mann-Whitney U test).
Results: The HD group had significantly less REM sleep (17.2% + 9.4 vs. 21.3% + 4.6; $p = 0.032$), more NREM sleep (82.8% + 9.4 vs. 78.7% + 4.6; $p = 0.032$), and a higher brief arousal index (30.7 + 22.1 vs. 2.4 + 4.1/hour; $p < 0.001$) when compared to CKD controls. The respiratory disturbance index was also higher in the HD group (9.9 + 18.4 vs. 1.9 + 4.0), a finding that approached statistical significance ($p = 0.061$). Although not statistically significant, the HD group had a longer sleep latency (35.0 + 36.9 vs. 19.1 + 17.1 minutes), lower sleep efficiency (77.5% + 13.9 vs. 84.0% + 11.7), reduced total sleep time (327.2 + 57.4 vs. 363.5 + 81.7 minutes), longer REM latency (138.7 + 101.4 vs. 93.7 + 55.6 minutes), and higher periodic limb movement index (29.4 + 43.9 vs. 6.1 + 8.2/hour) than controls subjects.
Conclusion: These results indicate that patients receiving HD have more disturbed sleep than age and gender matched controls who are metabolically comparable but not yet receiving treatment. The acute effects of HD may interact with the homeostatic and circadian regulation of sleep to induce this disruption, possibly facilitating the expression of sleep apnea and periodic limb movement disorder so common in this population.

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Polysomnographic Profile Of Patients With Neuropathic Pain And Self-Reported Sleep Disturbance

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Introduction: Pain contributes to disturbed sleep, and disturbed sleep also exacerbates the experience of pain. However, the determination of sleep disturbance may be problematic, as self-reported sleep disturbance does not always concur with polysomnographic (PSG) assessment, either in the general population or in a model of chronic inflammatory pain. This study was undertaken to examine the degree to which self-reported sleep disturbance among patients with neuropathic pain corresponds with PSG findings and to better define the nature of sleep disturbance in this population.
Methods: 35 patients who had neuropathic pain-due to either diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN)-for ≥ 3 months that was rated as moderate to severe (SF-MPQ VAS≥40 mm) and who also reported disturbed sleep in the previous 4 weeks underwent 2 consecutive nights of in-home PSG. Mean scores were then compared with scores of patients with primary insomnia and healthy volunteers without insomnia, as reported in the literature.
Results: Objective sleep disturbance was confirmed by PSG in 34 of the 35 patients. Their mean age was 66.3 years (n=34). Ten had sleep apnea (apnea index>10), 13 had both prolonged sleep latency and sleep fragmentation (LPS>20 min, WASO>20 min, TST<420 min), and 11 had sleep fragmentation despite normal sleep latency (WASO>20 min, TST<420 min). Across all 35 patients, mean (SD) TST was 319.8 (77.1) min, LPS was 34.2 (44.0) min, and WASO was 106.7 (53.1) min. Mean sleep efficiency (SE) was 67.7 % (14.9). PSG findings reflected sleep disturbance more severe than that previously reported in primary insomnia, including substantial reduction in both SE and TST, increased LPS, and substantially increased WASO.
Conclusion: 34 of 35 patients with neuropathic pain and self-reported sleep disturbance had PSG evidence of sleep disruption, especially with severe sleep fragmentation, compared with patients with primary insomnia. Proactive identification and amelioration of sleep disturbance among neuropathic pain patients may positively impact their well-being and quality of life. Further study of sleep disturbance in neuropathic pain is warranted.

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Disturbed Sleep, Insomnia, and Neuropathic Pain

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Introduction: The relationship between sleep disturbance and chronic pain is well documented, with a variety of pain conditions leading to reports of disturbed sleep and sleep deprivation leading, in turn, to a decrease in pain threshold. Polysomnographic (PSG) studies in patients with chronic pain due to rheumatologic conditions have reported the degree of sleep disturbance being less severe than is typically self-reported by patients. This study was undertaken to determine the degree to which self-reported sleep disturbance in a neuropathic pain population predicts PSG evidence of insomnia.
Methods: We report on a group of 35 patients with neuropathic pain due to either postherpetic neuralgia (PHN) or diabetic peripheral neuropathy (DPN). All subjects reported disturbed sleep and neuropathic pain for at least 3 months prior to assessment. Two consecutive nights of clinical PSG were performed after patients were discontinued from all hypnotics, antidepressants, benzodiazepines, AEDs, and opioids for 7 days.
Results: Using a definition of insomnia often used in hypnotic trials (ie, sleep latency or wake after sleep onset of greater than 20 minutes and at least 1 hour of wakefulness during an 8-hour recording), 34 of the 35 patients met objective PSG criteria for insomnia. Interestingly, 10 of the subjects had sleep apnea with Apnea-Hypopnea Index (AHI)>10. The PSG of the remaining subject revealed marked elevation of wakefulness, transient arousals, and sleep architecture disturbance (less slow wave and REM) compared with historical age-matched normals as well as patients with other pain conditions reported in the literature. In this population, self-reported sleep disturbance was generally corroborated by objective PSG evidence.
Conclusion: Patients with moderate to severe neuropathic pain and self-reported sleep disturbance demonstrate objective PSG evidence of disturbed sleep, meeting objective criteria for insomnia. Disturbed sleep, sleep loss, and insomnia have been shown to be associated with decreased pain tolerance, increased risk of depression, and decreased quality of life. Therefore, these data emphasize the importance of addressing self-reported sleep disturbance in neuropathic pain patients.

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Frequency Of "Problems With Sleep" Identified Through Screening Patients With Cancer

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Introduction: Introduction: The incidence of sleep disorders in patients with cancer has not been systematically studied. In cross-sectional studies, the prevalence of problems sleeping is high. However, most of these studies included patients who were already receiving treatment for cancer or had recently completed therapy. To determine the prevalence of sleep problems, we incorporated a question about sleep in a screening form completed by patients at their initial evaluation, prior to institution of therapy.
Methods: Methods: At their initial visit, all new patients evaluated by faculty in the Division of Medical Oncology at Eastern Virginia Medical School complete a self-report, one-page screening form that addresses physical, social, psychological, and financial needs of the patient. We incorporated "problems with sleep" to a previous screening form that already included "fatigued (feeling tired) within the past 24 hours."
Results: Results: Between February 2002 and December 2003, 134 forms have been completed; 93 were female and 41 male. The median age is 54 years; Range 24-84 years. The primary diagnosis was: breast cancer -73 (54%), lung cancer- 13 (10%), head and neck cancer -8 (6%), lymphoma - 6 (4%), colorectal cancer -6 (4%), and other - 28. The most common problems identified were: "problems with sleep" - 31 (23%), "feeling depressed or blue" 19 (14%), pain (12%), and "fatigued (feeling tired) within the past 24 hours" - 14 (10%). Problems with sleep problem were more common in women 27 (29%) than men 5 (12%). Problems with both sleep and fatigue were noted by 10 patients; 9 (11%) females and 1 (2%) male.
Conclusion: Conclusion: Similar to studies in the population at large, our data suggest that problems with sleep are common in patients with cancer and are more common in women than men. To determine the impact of the cancer diagnosis and its treatment, we have initiated prospective clinical trial using sleep diaries and fatigue scores to confirm

the high incidence of sleep problems and to determine the nature of these problems.

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Self-Reported Sleep Disturbance In Stomach Cancer Patients Who Are Undergoing Chemotherapy In Korea

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Introduction: Sleep disturbance is a prominent complaint in cancer patients, having multiple potential negative impact. Research related to sleep disturbance in cancer patients has been conducted mostly in the U.S. Yet there is little research on the prevalence or symptom presentation of sleep disturbance with Korean cancer patients. In Korea, cancer is a leading cause of death for men and women with stomach cancer. The purposes of the study are to: 1) examine sleep quality and characteristics in stomach cancer patients who are receiving chemotherapy; 2) describe the relationships between other symptoms(fatigue, depression) and sleep disturbance; and 3) examine the impact of patients sleep quality and other symptoms on quality of life.
Methods: A descriptive, cross-sectional design was used to obtain data from convenient sample of 103 stomach cancer patients (71 males, 32 females) who are undergoing chemotherapy at an outpatient clinic at university teaching hospital. Study participants completed questionnaires on the day of treatment: demographics, Pittsburgh Sleep Quality Index (PSQI), Center for Epidemiological Studies-Depression (CES-D-Korean), Lee Fatigue Scale(LFS), and Quality of Life-Cancer(QOL-C).
Results: The average age was 52.4 (SD=10.1), 92% married, 59% high school education, and 29% working as part time or full time. Cronbach alpha coefficient for the PSQI was .68. The CES-D alpha coefficient was .83. The LFS alpha coefficient was .89. The QOL-C alpha coefficient was .81. PSQI global sleep quality ranged from 2-15, with a mean of 6.95 (SD=2.67), as reported similarly in breast and other cancer studies. Carpenter(1999) suggested that a PSQI score of 8.0 might be a more appropriate cutoff score to indicate poor sleep quality in cancer populations and 22% of our sample had a PSQI score greater than 8.0. There was no significant difference in sleep quality between males and females. The seven components of PSQI were similar to those reported previously. A t-test analysis revealed statistically significant differences in fatigue levels and depression scores by gender. Females reported significantly more fatigue (mean=70.61, SD=13.38) than males (mean=59.27, SD=18.06). Females reported a higher depression score (mean=20.69, SD=9.06) than males (mean=14.52, SD=8.39). Significant positive correlations were found between fatigue and depression ($r=.46$, $p<0.01$), and depression and global sleep quality ($r=.22$, $p<0.05$). Fatigue and depression were negatively correlated with quality of life ($r=-.43$, $r=-.56$, $p<.01$). No significant correlation between fatigue and sleep was found. Multiple regression analysis revealed that the symptoms of depression and fatigue explained 35% of the variance in quality of life, with the largest proportion of the variance explained by depression [$F(5,97)=11.29$, $p<.005$].
Conclusion: This study provides baseline data on Korean stomach cancer patients sleep and their relationship with other symptoms, with these analyses being similar to previous studies of sleep disturbance in cancer patients. However, using subjective measurement of sleep may not give a complete picture of sleep patterns in Korean cancer patients. This is due, in part, to cultural differences based on Confucian ethics. Further study is needed using objective measurements of sleep in a longitudinal design in this population.

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Plasma IL-6 and TNFα Levels are Elevated in Polycystic Ovary Syndrome Independent of Obesity and Sleep Disturbance

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Introduction: Pre-menopausal women with polycystic ovary syndrome (PCOS) are at a much higher risk for development of sleep apnea and daytime sleepiness compared to controls. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) are elevated in sleep apnea and disorders of excessive daytime sleepiness (EDS) and promote insulin resistance, a central abnormality of PCOS. The purpose of this study was to test whether PCOS is associated with an increase of plasma cytokines (IL-6 and TNFα) independently of obesity and sleep apnea.
Methods: Forty-two obese women with PCOS, 17 BMI-matched, obese controls, and 15 normal-weight controls free from apnea participated in the study that included one 8-hour nighttime polysomnography, cytokine plasma concentrations, and insulin resistance indices.
Results: PCOS women complained of EDS (moderate to severe) more frequently than the two controls groups (both $P < 0.05$). PCOS women had higher plasma concentrations of IL-6 and TNFα than obese controls, who had intermediate values, or normal-weight controls, who had the lowest values ($P < 0.05$ between PCOS and normal-weight controls). Both IL-6 and TNFα values positively correlated with BMI ($P < 0.05$). The strongest predictors of plasma IL-6 levels were PCOS with the largest effect size ($P < 0.05$) and obesity with an intermediate effect size compared to normal-weight controls. Furthermore, within the PCOS group, TNFα correlated positively with fasting plasma insulin levels and negatively with glucose-to-insulin ratio, whereas IL-6 correlated positively with fasting plasma glucose levels.
Conclusion: We conclude that IL-6 and TNFα are elevated in women with PCOS independently of obesity and sleep apnea, may mediate EDS and fatigue frequently present in PCOS, and may predispose them to the development of sleep apnea at a later stage. Finally, hypercytokinemia may represent a pathophysiologic link to insulin resistance and cardiovascular morbidity associated with PCOS.

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Diagnosis and Treatment of RLS Among 737 Hemodialysis Patients

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Introduction: A lower prevalence of RLS among older African-Americans than among Caucasians on hemodialysis (HD) has been reported. Furthermore, previous reports have indicated a decreased sensitivity of the IRLSSG questions among HD patients due to a tendency for them to underestimate or underreport RLS symptoms except for the most severe cases.
Methods: A sleep history was adminstered in person to 792 adult HD patients (51% male) in southeast Michigan and northern Ohio from May

to August 2003. Data from African-Americans (60%, n = 475) and Caucasians (33.1%, n = 262) only were analyzed for the purpose of this report. Mean age was 61.0 + 15.0 years. Participants were on dialysis for an average of 3.5 + 3.62 years. Patients were ineligible for the study if they were under the age of 18, cognitively impaired as determined by staff members familiar with the patient's status, or if dialyzing in isolation units.
Results: Twenty-five percent of the sample met IRLSSG diagnostic criteria. Those meeting criteria for RLS were more likely to be female (X2 = 6.30, p = .008) and tended to be white (X2 = 2.22, p = .08). Only 8.1% of the sample reported having been diagnosed with RLS and 2.0% were being treated for the condition. Among those meeting criteria for RLS no racial or gender differences were found in probability of reporting leg twitching or jerking during sleep as per their bed partner. Caucasians (X2 = 6.33, p = .01) and men (X2 = 3.07, p = .05) were significantly more likely to have been diagnosed with RLS. Next we compared 3 independent groups, those with the diagnosis (n = 50) [DX], those meeting criteria but not diagnosed (n = 141) [MC], and those with no RLS symptoms (n = 408) [NO]. There were no significant differences in reported frequency of RLS symptoms the DX and MC groups. Furthermore, the DX and MC groups were not significantly different on multiple questions based on DSM-IV insomnia criteria, such as problems with sleep initiation, maintenance, and sleep not being refreshing. However, on an overall rating of perceived severity of sleep problems over the last 3 months the DX group reported more severe problems than the MC group (t = 2.08, p = .04). Finally, the MC and NO groups were compared. The MC group was significantly worse on every DSM-IV-based insomnia question than the NO group.
Conclusion: In this study we found a high prevalence of RLS despite the likelihood that these questions underestimate the prevalence in this population. Based on this, we conservatively estimate that 17% of HD patients with RLS go undiagnosed and 23% with RLS are untreated despite the presence of significant symptoms. Even in this population receiving close medical care, RLS remains overwhelmingly undiagnosed and untreated.

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Sleep Patterns Of Stable Heart Failure Patients Compared With Healthy Controls

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Introduction: Sleep disorders are common among patients with heart failure. However, few data are available on the characteristics of sleep occurring in patients living in their home environments or the magnitude of sleep disturbance relative to healthy people of similar age and gender. The purposes of this study were to compare the behavioral attributes of sleep patterns among stable heart failure patients to the sleep patterns of a healthy comparison group.
Methods: The sample included 65 stable heart failure patients who had ejection fractions < or = 35% and lived in their home environments and a group of 62 community-dwelling healthy controls. Participants wore wrist actigraphs (Actiwatch, Minimitter, Inc.) for three days and completed daily sleep diaries, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and the SF-36. Sleep was scored using software provided by the manufacturer. The three days of actigraph and sleep diary data were averaged. Physical function and emotional wellbeing component scores were calculated from the SF-36.
Results: Sixty-five heart failure patients (M age = 58.51 + 12.84 years, 42 male, 23 female, New York Heart Class II-IV, ejection fraction < 35%), and 62 healthy adults (M age = 54.5 + 10.48 years, 29 male, 33 female) participated in the study. Heart failure patients had lower physical function ($p < .001$), but no poorer mental health scores on the SF-36 than the health comparison group. Heart failure patients had significantly poorer self-reported sleep, measured by the PSQI (7.17 + 3.29 vs. 5.35 + 2.13, $p < .01$), more frequent awakenings (51 vs. 41, $p < .01$), lower sleep efficiency (77% vs. 86%, $p< .001$), more prolonged sleep latency (40.51 + 57.31 vs. 15.64 + 18.55, $p < .01$) and shorter sleep bouts (9.11 + 3.45 vs. 11.61 + 5.42 minutes, $p < .01$) than the healthy comparison group. Actigraph-measured (6.39 + 1.72 vs. 6.59 + .96 hours) and self-reported sleep duration and the daily diary (Visual analog scale) measure of sleep quality did not differ between groups. There were no differences between groups on awakenings to use the bathroom or number of pillows used at night. Thirty-nine percent of the heart failure patients scored higher than 10 on the Epworth scale, compared with 14% of the health comparison group, $p < .01$. Men scored higher on the Epworth scale than women (M = 8.54 + 5.0 vs. 6.25 + 4.88, $p< .05$. However, there was no gender by study group (patient vs. control) interaction. There were no correlations between age and any of the sleep variables.
Conclusion: Stable heart failure patients living in the home environment have significantly poorer objective and self-reported sleep quality and more excessive daytime sleepiness than a comparison group of healthy study participants. However, there does not appear to be a difference in total sleep duration.

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Effects of Esomeprazole and Placebo On Relief of Moderate to Severe Nighttime Heartburn, Sleep Disturbance and Sleep Quality In Patients With GERD: A Multicenter, Randomized, Controlled Trial

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Introduction: Up to 80% of patients with gastroesophageal reflux disease (GERD) report sleep disturbance. This study compared the effects of esomeprazole (20 or 40 mg once daily) and placebo on relief of GERD-related moderate/severe nighttime heartburn, sleep disturbance and sleep quality.
Methods: Patients aged 18 to 85 years with symptomatic GERD who met the following criteria were enrolled in a randomized, prospective double-blind study: history of erosive esophagitis or episodes of heartburn or acid regurgitation for ≥ 3 months; history of GERD-associated sleep disturbance (e.g. trouble falling asleep, frequent awakening, poor sleep quality) for >1 month; sleep disturbance and moderate to severe nighttime heartburn on ≥ 3 of the last 7 days of the run-in period. Patients with conditions (other than GERD) known to affect sleep were excluded. Sleep medication was allowed if usage was stable (≥ 3 months) and expected to remain stable throughout the study. Patients were randomized to esomeprazole 20 or 40 mg or matched placebo qAM for 4 weeks. Daily diary card was used to assess nighttime heartburn symptom severity (none, mild, moderate, severe). Sleep disturbance assessed by "yes/no" response to the question "Did you have trouble sleeping last night due to your heartburn or other symptoms of GERD?". Sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) questionnaire at baseline and end of week 4. PSQI assessed sleep over the previous month on 7 dimensions (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use

of sleeping medication, and daytime dysfunction), each rated on a 4-point scale (0 to 3, with 3 indicating more profound effect), which are added together to give a global score, with higher scores representing worse sleep quality. The primary endpoint was patient-recorded relief of nighttime heartburn, defined as diary card response of none on ≥ 6 of the last 7 days in the study (allowing for one response of mild). Secondary endpoints were the percentages of patients with relief of sleep disturbance on ≥ 5 of the last 7 days in the study and changes in global PSQI scores.

Results: Intent-to-treat population consisted of 650 patients. Percentages of patients with relief of nighttime heartburn were 8%, 44%, and 45% for placebo (n=221), esomeprazole 20 mg (n=220), and esomeprazole 40 mg (n=209), respectively. Percentages of patients with relief of sleep disturbance were 55%, 81%, and 85% for placebo, esomeprazole 20 mg, and esomeprazole 40 mg, respectively. PSQI change from baseline to week 4, -2.0 for placebo (n=214) versus -3.8 esomeprazole 20 mg (n=214) and -3.5 esomeprazole 40 mg (n=204). All comparisons statistically significant versus placebo (P<0.0001). Percentage of patients with good sleep (PSQI < 5) at baseline versus week 4 was 13.6% vs 37.0% placebo, 16.8% vs 57.5% esomeprazole 20 mg and 19.6% vs 51.9% esomeprazole 40 mg.

Conclusion: In this randomized controlled trial in patients with moderate to severe nighttime heartburn and GERD-related sleep disturbance, esomeprazole provided highly significant improvements in the relief of nighttime heartburn, the relief of sleep disturbance and sleep quality as detemined by a validated instrument.

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The Impact of Acupuncture on Nocturnal Hot Flashes and Sleep

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Introduction: Since the publication of the Women Health Initiative study in 2002, many postmenopausal women taking Hormone Replacement Therapy (HRT) discontinued use and were left with few known effective methods of treatment. Although postmenopausal women often seek acupuncture to treat their hot flashes, the present study is the first placebo controlled study to evaluate its efficacy. We hypothesized that active acupuncture would reduce nighttime hot flashes more than placebo acupuncture, and that a reduction in nighttime hot flashes would in turn improve the overall quality of sleep.

Methods: Twenty postmenopausal women were randomized to receive eight weeks of either active or placebo acupuncture treatment. Placebo acupuncture was provided with sham needles that do not penetrate the skin (single blind). Participants were between the ages of 45 and 65 (mean=56.0, SD=3.9) and experienced an average of at least seven moderate to severe hot flashes per 24-hours. Exclusion criteria were: concurrent serious medical condition, other treatments for hot flashes (including HRT and SSRIs), and abnormal thyroid levels. Postmenopausal status was confirmed with plasma estradiol and FSH levels. The Pittsburg Sleep Quality Index (PSQI) was filled out at intake and at the end of the study. Participants also kept daily logs of the frequency and severity of daytime and nighttime hot flashes experienced throughout the entire study.

Results: Although not selected for poor sleep, the majority of women (17/20) had a baseline PSQI score above the clinical diagnostic cutoff of five. Nocturnal hot flashes decreased from a weekly average of 8.3±3.5 at baseline to 3.0±2.4 at the end of the active treatment (F=12.84, df=1, p=0.007). Nocturnal hot flashes were also reduced with placebo treatment from 7.5±3.3 to 4.16±3.7 (F=6.21, df=1, p=0.034). In a repeated measures analysis of variance, with treatment group as between-subjects factor, the treatment group by time interaction was not statistically significant (F=0.9, df=1, p=0.36). However, the estimated effect size for the change in nocturnal hot flashes was 0.75 for the placebo group and 1.17 for the active acupuncture group. Total PSQI score significantly decreased from baseline, regardless of treatment group (from 10.6 to 8.1, p=0.012). Even though the correlation between improvements in nocturnal hot flashes and improvement in total PSQI scores was not significant, the correlation between improvement in nocturnal hot flashes and improvement in the overall sleep quality item of the PSQI was approaching significance (r=0.43, p=0.07).

Conclusion: Improvement in nocturnal hot flashes was larger in the active acupuncture than in the placebo group, but the difference was not statistically significant. Given the high placebo response in most controlled treatment studies for hot flashes and the group difference in the effect sizes, it is likely that the observed advantage was not statistically significant because of the study's small sample size and low statistical power. Acupuncture designed to reduce hot flashes also improves sleep and might, therefore, be a useful adjunct in the treatment of insomnia in postmenopausal women with nocturnal hot flashes.

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The Role of Depression in Sleep and Gastrointestinal Complaints in Patients with Irritable Bowel Syndrome

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Introduction: Depression and sleep complaints are commonly noted in patients with irritable bowel syndrome (IBS). Depression alone is often associated with sleep complaints, but the extent to which these cormobidities may overlap in patients with IBS is not clear. The objective of the current study was to examine the degree to which depressive symptomatology may account for sleep abnormalities in patients with IBS.

Methods: 70 IBS patients who met Rome II criteria for IBS, as well as 21 normal volunteers, participated. After initial telephone screening, participants came to our facility on two occasions. During the first visit, the diagnosis of IBS was established, a physical exam was performed, and participants filled out several questionnaires. On the second visit, a polysomnographic study was performed to obtain object measures of sleep parameters. IBS patients were stratified into two groups based on their Beck Depression Inventory-II scores. 44 IBS patients with depressive symptoms (IBS + DS) were compared to 26 IBS patients without depressive symptoms (IBS - DS), and 21 healthy controls. Subjective sleep quality was assess by the Pittsburgh sleep Quality Index (PSQI). Gastrointestinal symptom severity was assessed via an 18 item questionnaire, and all participants completed the Spielberger State/Trait Anxiety Scale.

Results: IBS + DS patients had a significantly higher score on the global PSQI scale (P < .05), as well as on all subscales (p < .01) compared to both the IBS - DS and healthy control groups. This indicates the the IBS + DS group reported significantly poorer sleep quality, longer sleep latency, less sleep duration, greater number of sleep disturbances, more daytime dysfunction, and taking more sleep medication than IBS - DS group and healhty controls did. As a whole, IBS groups had a significant prolongation of the latency to the first REM period (IBS-DS=122 SD 10, IBS+DS=126 SD=13, controls=85 SD-9). No other group differences in sleep architecture were observed. IBS + DS patients also had signifi-

cantly higher scores on gastrointestinal symptom severity (P < .01). In addition, an analysis of covariance was performed testing PSQI scores after controlling for anxiety level. This analysis revealed that the IBS + DS group continued to have worse subjective sleep quality than IBS - DS group (P < .05).
Conclusion: 1. Depression appears to play a major role in the appearance of sleep complaints in IBS patients. 2. The latency to REM sleep is delayed in all IBS patients, includng those with depressive symptomatology, which is counterintuitive based on previous research showing clinically depressed patietns with an abbreviated REM onset latency. 3. The impact of depression on sleep symptoms appears to be independent of reported anxiety level.

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Characterizing Sleep Disorders: Male-Female Variations and Similarities

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Introduction: In medicine, the vast majority of sex difference research has focused on cardiovascular disease which clearly demonstrated the critical need for sex specific treatment to ensure the best possible outcomes for all. Other medical research areas are in the beginning stages of recognizing the importance of investigating these differences. Research focusing on sleep disorders (SD) is no exception as few studies have focused on sex as a variable. SD result in prolific health problems: many of which the scope has yet to be identified because of significant rates of under or inadequate diagnoses. Diagnosis is complicated by a multitude of intervening variables that range in effects from disguising the presence of SD to inadequate understanding of the relationships shared by other health problems and SD. Investigations are further restricted by difficulty in acquiring valid data from patients whose diagnosis is based on a complete nocturnal polysomnography (NP) and/or multiple sleep latency test (MSLT). Thus, anecdotal accounts prevail in the absence of professional examination and testing. Research in this area has the potential of advancing knowledge about variables associated with SD, revealing patterns of symptomatology, illustrating effective treatment modalities, and ascertaining relevant covariances. It is our goal to help identify common symptomatic patterns in general and those that are specific to men and to women.
Methods: We assembled a team composed of professionals from a broad spectrum of specialty areas and constructed a 111-item questionnaire to assess sleep habits, sleep observations, past medical history, prior treatment approaches for SD, social information, and medications. We used the questionnaires in conjunction with other standard patient questionnaires, nocturnal polysomnography (NP) studies, multiple sleep latency tests (MSLT), and medical chart reviews of patients with SD. We then constructed a database comprised of 305 measures collected in 13 categories.
Results: Of the 316 participants, 122 were female with a mean age of 47.63 (range, 1-81 years) and an average weight of 206 (range, 20-406 pounds) while 194 were male with an average age of 49.78 (range, 2-88 years) and an average weight of 222 pounds (range, 48-757). We compared men and women with SD to find patterns of similarities and differences. An example of findings revealed by chi square analysis indicated that proportionally more men were diagnosed with sleep apnea, stopped breathing during sleep, and were more likely to complain of headaches. Proportionally more women were diagnosed with diabetes, asthma, muscular problems (such as fibromialgia), genitourinary problems, obesity, allergies, and thyroid disease. Women were also more likely to report: problems with memory for detail, feeling stressed, trouble with anxiety, being depressed, experiencing choking sensation, and being sleepy during the day. Analysis also revealed different pain locations, patterns of sleepiness, reports about causes of stress, and effects of SD on their lives.
Conclusion: Although men and women shared some patterns of SD findings they were disparate in others. Given the critical role of sleep in maintaining good physical and mental health, it is imperative that more research attention be focused on illuminating the complex web of variables associated with SD.

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The Effect of Overnight Sedation on Daytime Sleep-Wake Behavior in the Intensive Care Unit

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Introduction: Intensive Care Unit (ICU) patients have abnormal circadian rhythms and sleep-wake cycles, as has been documented by Freedman and others. These abnormalities may have consequences for clinically important variables such as pulmonary muscle strength, drug efficacy, and psychological well-being. It has been suggested that a normal sleep-wake cycle could be restored by overnight sedation, but this hypothesis has not been tested experimentally. To address this issue, we evaluated the effect of overnight sedation on daytime sleep-wake behavior in ICU patients.
Methods: We studied n=15 a-septic patients of age 62±8 (range 50–79), with APACHE III scores of 57±22 (range 29–90), over a period of 72h in the ICU. The first 24h period involved no intervention and was considered to be a baseline period. The second 24h period involved continuous overnight propofol 2% infusion, from 22:00 until 06:00 the next day. A Ramsay score of 3–4 (i.e., patient responding to commands only; brisk response to light glabellar tap) was considered the target sedation level, and the infusion rate was titrated accordingly. The third 24h period was a repetition of the second. EEG recordings were made throughout the 72h of the study.
Results: Infusion rates were 2.9±0.6mg/kg/h in the second 24h period and 3.0±0.4mg/kg/h in the third 24h period (not significantly different). During the baseline period, patients exhibited 7.3±3.0h (mean±s.d.) of total sleep time (TST). This included 3.4±1.5h of TST in the period from 06:30 until 22:00; that is, approximately 50% of sleep in the 24h baseline period occurred during the day. Using a one-sided paired t-test, we found no significant reduction for the average amount of daytime TST in the two intervention periods compared to the baseline period (p=0.78). There was no significant difference in TST between the first and the second intervention periods (p=0.11). There also were no significant differences among the baseline and intervention periods with respect to the various sleep stages.
Conclusion: Overnight sedation did not result in decreased daytime sleep in our sample of ICU patients. Thus, we found no support for the assumption that overnight sedation can restore normal sleep-wake cycles in these patients. This finding may have implications for the extent to which overnight sedation is clinically beneficial in the ICU.

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Changes in Sleep and Fatigue During Radiation for Breast Cancer

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Introduction: Cancer-related fatigue is a significant clinical issue.

When it occurs and its pattern and severity are not evident from prior studies and few studies have examined changes in sleep that may contribute to fatigue. The purpose of this study was to describe changes in sleep and fatigue during radiation therapy (RT) from pre-radiation simulation to the end of RT. We previously reported on men with prostate cancer and the results presented here include women with breast cancer under a similar protocol.
Methods: Data were collected from 78 women; mean age was 54.7 (range 27-85 yrs). There were 52 White, 10 Black, 9 Asian, 4 Hispanic, and 1 Other; 41 were Stage 1, 27 were Stage 2, and 8 had Stage 3 breast cancer. Most (74%) had a lumpectomy, and 56% (n=43) also received chemotherapy. Sleep quality on the Pittsburgh Sleep Quality Index was 7.58+4.0 at baseline. Wrist actigraphy (Ambulatory Monitoring, Inc.) was used to estimate sleep for 48 hrs each week. Other measures included the Lee Fatigue Scale (completed morning and evening) with scores ranging from 0 to 10. Data from 2 nights were averaged and repeated measures analyses of variance were used to test within-subject changes over time (baseline simulation week, 5 weeks of RT, and first week after RT was completed). Variables included: time in bed (TIB), total sleep time (TST), wake after sleep onset (WASO), and evening/morning fatigue. Post-hoc Scheffé tests were used to determine peak changes.
Results: A total of 65 women had complete fatigue data and 51 had complete actigraphy data for analyses. Evening fatigue increased ($F=12.37$, $p<.001$) over the 5 weeks of RT (from 4.5 to 5.6), and dropped at completion of RT (3.3+2.15). Morning fatigue also increased ($F=4.4$, $p=.04$) over time (from 2.8 to 3.4). TIB increased slightly over time, with a peak at the third wk of RT (505+68 mins). TST also peaked the third wk (430+65.2 mins), and was lowest during the first week of RT (411+74.3 mins) and during the first week after completing RT (405 + 91.4 mins). WASO was lowest at simulation (10.3+7.8%) and was stable at 11.6% during the first three weeks of RT. Their high perceived sleep disturbance (45.5+21.8) at baseline remained unchanged.
Conclusion: TIB was higher in this sample (8.5 hrs) compared to our previous group of men with prostate cancer undergoing RT (8.0 hrs). TST was also higher (7.0 hrs) and peaked during the third week compared to the men (6.5 hrs) who peaked during the fourth week of RT. WASO was lower for these women (10.3 to 11.6%) compared to men with prostate cancer who baseline WASO of 15% that increased to 20% during the sixth week of RT. Similar to the men, morning and evening fatigue peaked during the fifth week of RT for women. Despite having more sleep time and less wake time, this group of women perceived more severe fatigue and higher sleep disturbance at all time points compared to the men with prostate cancer under a similar protocol.

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The Effect of Powerful acid Suppression on Sleep Related Gastroesophageal Reflux

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Introduction: Persistent gastroesophageal reflux (GER) during sleep has been strongly implicated in the complications of GER and has been shown to occur predominantly with brief arousal responses. Powerful acid suppression using proton pump inhibitors (PPIs) are commonly utilized method to treat GER disease (GERD). In general, this is effective in reducing both daytime and nighttime GER. However, non-acidic reflux may persist with potentially serious complications. The present study utilizes esophageal pH and impedence to identify both acidic and non-acidic reflux during sleep in response to powerful acid suppression by esomeprazole.
Methods: Twelve subjects with symptomatic GERD were studied under conditions of placebo and esomeprazole 40 mg b.i.d. All subjects kept a sleep log while on placebo for one week and esomeprazole 40 mg b.i.d. for one week. At the end of each week of treatment, subjects were evaluated via polysomnography (PSG), to include distal and proximal (pharyngeal) pH and impedence. Reflux events were determined to be associated with a brief arousal response if the reflux event occurred within 30 seconds after an arousal from slee. Reflux events without arousal from sleep, which occurred during stable sleep were also identified.
Results: 1. When collapsed across treatment conditions, arousal related and sleep related reflux events (acidic and non-acidic) were not significantly different (x=2.8 SD 4.5 vs. x-4.2 SD 3.4). 2. Sleep vs. arousal related reflux events were unaffected by whether the refluxant was acidic or non-acidic. 3. Esomeprazole treatment resulted in a significant decline in a sleep related reflux event (x-2.9 SD 2.1 vs. 1.3 SD 1.8)$p <$ 0.5 while there was no significant difference in the frequency of arousal related reflux events (x-1.7 SD 3.0 vs. x- 1.1 SD 1.9). 4. Total number of arousal responses were not significantly different nor were other sleep parameters such as sleep efficiency, total sleep time, and sleep onset latency when compared between placebo and drug conditions.
Conclusion: 1. When acidic and non-acidic reflux events are combined, arousals from sleep do not appear to enhance the occurrence of GER. 2. The persistence of arousal related reflux events, in spite of powerful acid suppression, suggests that these events may contribute to the poor treatment response noted in approximately 20% of GERD patients treated with PPIs.

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Efficacy Of Airbed Sleep System In Sleep Improvement In Chronic Low Back Pain

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Introduction: Research in order to assess the effectiveness of the treatment of chronic pain on sleep continuity and quality is relatively limited. This is particularly so with reference to mattress design.Recently, airbed systems have been introduced and claimed to produce better quality sleep. Testing of one such system on patients with chronic low back pain appeared to produce quite significant improvement on the subjective measures applied.The purpose of this project was to assess the response of individuals with chronic low back pain and disturbed sleep to a new airbed system, applying both subjective measures of sleep and health as well as sleep-related physiological changes.
Methods: Subjects had chronic low back pain of at least 2 months duration, pain that adversely affected sleep, and the perception of an uncomfortable mattress. Excluded were subjects with uncontrolled medical or other sleep disorders. Medications were unchanged. They were monitored at home with actigraphy as well as subjective measures of sleep and pain intensity using numeric and visual analogue scales, on their existing mattress, followed by 2 nights of in-laboratory polysomnography. A 4 week treatment phase followed, using the Nautilus Sleep System. This mattress consists of a plush top covering a visco-elastic foam layer over a dual interlocking system of variable support air chambers; the firmness is adjusted by the subject to a perceived optimal comfort level. Nightly actigraphy as well as subjective measures of sleep and pain intensity were collected, again followed by 2 nights of in-laboratory polysomnography. A 2 week post-treatment baseline was completed at home, again on their original mattress, collecting the same measures as initially. Averages of the parameters measured were calculated for the baseline week, last week of the treatment using the Nautilus Sleep System, and the post-treatment baseline. Functional Outcomes of Sleep,

SF-36, and Epworth Sleepiness Scales were collected, as well.
Results: 27 subjects, all adults, 15(55.6%) female 12(44.4%) completed the protocol. The age range was 41 - 60 years, mean 51.5. BMI mean was 29.5 (20 - 38). Evening, pre-lights out pain improved 30%, $p < 0.05$. This deteriorated on return to their original mattress. Subjective awakenings decreased 38%, $p < 0.05$. Arousals during polysomnography decreased 19%, barely missing significance at the 0.05 level. Subjective sleep fragmentation improved 24%, $p < 0.01$. Subjective depth of sleep improved 38%, $p < 0.01$. There was a 41% improvement in the AM rating of sleep quality, a 46% decrease in morning pain level, both significant at $p < 0.01$. Clinical Global assessments showed improvement in pain in 88.9%, sleep in 85.2% Polysomnography failed to demonstrate changes that were statistically significant. REM was mildly decreased. Improvement was seen in sleep efficiency, awakenings, and fragmentation index. ESS was normal throughout. FOSQ total average and subscales were mildly abnormal; all improved but changes were not statistically significant. SF-36 showed all scales were below average except general health; a trend toward improvement was seen in all scales but was not statistically significant. Scales deteriorated to baseline on return to the original mattress.
Conclusion: Use of the Nautilus Sleep System clearly produces a substantially improved perception in sleep continuity and depth as well as overall sleep quality. Morning discomfort in the group with sleep adversely affected by chronic low back pain was also substantially reduced. Even pain prior to lights out, and by implication possibly during the day as well, was notably reduced. The global measures are compatible with measured experiential improvements, supporting the beneficial effects of the bed system.

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Sleep Disorders in Fibromyalgia
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Introduction: The coexistence of disturbed sleep and fibromyalgia (FM) is well recognized. Less clear is whether there is any association between FM and primary sleep disorders. Our study examines sleep complaints, co-morbidities, medication history and salient polysomnographic (PSG) findings for patients with known FM.
Methods: The study was a retrospective chart review of patients, with known FM, evaluated at the Sleep Medicine Services over a ten-year period (August 1992 and July 2002). The chart review included the sleep history, documented co-morbidities and PSG findings.
Results: A total of 66 patients with FM were evaluated. There were 59 (89 %) women and 7 (11%) men. The median age was 50 years (range 21 to 82 years). Excessive daytime sleepiness (EDS) was the chief complaint in 44%, followed by fatigue 21%, insomnia 21% and pain 20%. Both snoring and frequent arousals were present in 77%. Restless leg syndrome was reported by 28%. The most common co-morbidities were GERD (24%), hypertension (20%), migraines (20%), depression (17%), hypothyroidism (15%), arthritis (12%), COPD (9%), chronic low back pain (6%) and cancer (3%). Fifty-five percent of patients were on antidepressants. PSG findings included a mean sleep latency of 31 minutes (range: 1.0 to 273). The mean % of slow wave sleep was 17.6 (range: 0.28 to 45.3). The average % of REM sleep was 13.6. The mean sleep efficiency was 72 (range: 0 to 94). Obstructive sleep apnea (OSA) (RDI>5/hr sleep) was found in 80%. The median RDI was 13.2 events/hr sleep (range: 0.5 to 185). Periodic limb movements in sleep (PLMS) were seen in 52% of patients. Of these, 18% had an arousal PLMS index >5/hr sleep.
Conclusion: In addition to the chronic pain issues in these patients, other more specific sleep complaints occurred with a high frequency. The noted co-morbidities (GERD, migraines and depression) also have a common association with poor sleep. Intrinsic sleep disorders were also frequent. These findings support that patients with FM should have careful questioning, and follow-up polysomnogram for symptoms suggestive of primary sleep conditions. Specific treatment for concomitant sleep disorders may improve quality of life in this patient population.

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Insomnia in HIV Infected Patients in the Era of Highly Active Antiretroviral Therapy (HAART)
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Introduction: Studies suggest that sleep disturbances in HIV infected patients may be related to immune system dysfunction. There is little data, however, on insomnia in HIV infected patients receiving HAART. We undertook a pilot study to evaluate the relationship between insomnia and HIV viral load (VL) and CD4 lymphocyte counts in patients on and off HAART.
Methods: 183 HIV infected subjects and 47 HIV negative controls were recruited upon presentation for routine medical outpatient visits. All participants completed questionnaires that included the Pittsburgh Sleep Quality Index (PSQI) and the Hospital Anxiety and Depression Scale (HADS). Medical records were reviewed for co-morbid conditions, medications (including HAART) and, for HIV infected patients, CD4 lymphocyte counts and HIV VL. All controls were screened and found negative for HIV antibody. The odds ratio (OR) for insomnia (defined by global PSQI score of > 5) as it relates to HIV status, CD4 counts and VL was determined using Cochran-Mantel-Haenszel Statistics.
Results: Preliminary analysis of data sets completed thus far yields the following: HIV positive subjects (n = 114) were more likely to have insomnia than HIV negative controls (n = 34), (OR 2.16 [95% CI: 0.9950 to 4.7039]; $P < 0.05$). Among HIV positive subjects, those with CD4 counts > 400 cells/mm3 (n = 22) were more likely to suffer from insomnia than those with CD4 counts < 50 cells/mm3 (n = 82), (OR 3.19 [95% CI: 0.9902 to 10.2609]; $P < 0.05$). HIV positive subjects with VL > 400 copies/mL (n = 42) were more likely to have insomnia than those with "undetectable" VL (< 400 copies/mL) (n = 29), (OR 4.67 [95% CI: 1.5683 to 13.8858]; $P = 0.004$). HIV positive subjects with VL above the median of 2,616 copies/mL (n = 36) were more likely to have insomnia than those with viral loads < 2,616 copies/mL (n = 35), (OR 5.22 [95% CI: 1.6446 to 16.5750]; $P = 0.0035$).
Conclusion: Our data confirms results of previous studies showing that HIV positive individuals are more likely to have insomnia than HIV negative controls. This data suggests as well that insomnia in HIV infected patients may be a result of the immune dysfunction that accompanies high VL. Our finding that subjects with the highest CD4 counts were more likely to have insomnia than those with the lowest CD4 counts is surprising, but may be explained by current HIV treatment standards as patients with higher CD4 counts are less likely to receive HAART and may therefore have higher, un-suppressed viral loads. Additional tabulation and analysis of our data will be necessary to answer this question and to determine the confounding effects, if any, of anxiety, depression and co-morbid medical conditions, as well as psychoactive and HAART medications.

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Sleep-Wake Disturbances and Associated Factors in Patients with Advanced Cancer

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Introduction: Introduction: Although sleep-wake disturbances are common in cancer patients, few studies have specifically focused on sleep and related factors in late stage cancer populations. Therefore, in order to begin a systematic examination of the sleep-wake patterns of patients with advanced cancer, we studied a sample of patients with late-stage lung and colorectal cancer and examined subjective nocturnal sleep quality, daytime sleepiness, and related demographic and clinical factors.
Methods: Methods: The sample included 79 medical oncology outpatients (48% female) with a mean age of 61.08 (SD 11.67, range 28-84) who had a diagnosis of stage IV colorectal (n = 36) or either stage IIIB-IV non-small cell or extensive small cell lung cancer (n = 43). All were cognitively intact (Mini-Mental State Examination >24), had no previous history of PSG diagnosed sleep disorder, no known cerebral metastases or other neurologic disease, or DSM IV mood, anxiety or psychotic disorder. Subjects completed the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). Clinical and demographic factors were obtained via interview and record review. Group differences in sleep-wake variables were analyzed with ANOVA. Bivariate correlations between sleep variables, demographic, and clinical factors were conducted.
Results: Results: Subjects experienced nocturnal sleep disturbance as evidenced by a mean PSQI global score of 8.58 (SD 3.59, range 2-17). The most frequently reported disturbances included nocturnal awakenings, nocturia, cough, breathing difficulty and pain. In addition, 40% of subjects had an ESS score of 10 or more (mean 8.52,SD 4.33, range 0-21) indicating significant daytime sleepiness. Daytime sleepiness was associated with nocturnal sleep quality (r=.274; p=.015). Group differences in subjective sleep quality and daytime sleepiness were not statistically significant. However, lung cancer diagnosis was associated with disturbances in breathing (rs = -.246;p=.029), cough/snoring (rs = -.359; p=.001), and daytime dysfunction (rs=-.326; p=.003). There was no significant association between demographic variables and subjectively reported nocturnal sleep or daytime sleepiness. Functional status as measured by the Karnofsky Performance State was negatively associated with both global PSQI (rs = -.364;p=.001), and ESS scores (rs = -.243;p=.031). No other clinical variables were associated with nocturnal sleep quality. However, the number of comorbid conditions (rs = .359;p=.001), in particular CAD (r s = .316;p=.005) and CHF (rs = .227;p=.044), and the number of non-antineoplastic medications (rs = .415;p<.0001) were associated with daytime sleepiness.
Conclusion: Conclusions: These preliminary results are consistent with previous findings that sleep-wake disturbances are prevalent in patients with advanced cancer and may be related to functional status and the number of concurrent pathologies. Furthermore, daytime sleepiness may significantly impact nocturnal sleep. As we continue to examine associations between demographic and clinical variables and subjective nocturnal sleep quality and daytime sleepiness we will gain a greater understanding the factors that contribute to sleep-wake disturbances in this population.

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Bright Light: Lateralized Effects on the Regional Cerebral Blood Flow in Patients with Seasonal Affective Disorder and Healthy Controls

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Introduction: Bright-light treatment is a safe and effective phase shifting and antidepressant agent. We have previously reported that one session of bright-light activates the anterior insular/ ventrolateral prefrontal cortex (AI/VLPFC) bilaterally and the right lingual cortex, and deactivates the right cerebellum in both patients with seasonal affective disorder and healthy controls. Given the abundant literature on hemispheric laterality in emotional regulation and dysregulation, we now analyze how bright-light changes asymetry in regional cerebral blood flow (rCBF)
Methods: Cerebral blood flow was measured using O15 water and PET with arterial input functions in 15 depressed patients with SAD and 15 matched healthy controls. Subjects signed informed consent after a full explanation of the study, which was approved by the intramural NIMH. Nine scans were performed at 12-minute interval. Three scans were performed at baseline (dim light). The subsequent 6 scans alternated between the on-light (three scans) and post-light (three scans off-light) conditions. Light was administered with a cool-white bright light device suspended above the scanner and delivering approximately 8,200 lux at the level of the eye. The average cumulative duration per light scan was 29.7 minutes. Mood was measured with the NIMH mood scale. Effects of light on regional CBF (rCBF) were assessed by comparing normalized blood flow in the on light and post-light conditions relative to the baseline condition, using SPM 99. The cerebral asymmetry index (R-L)/(R L) in rCBF in regions where we have previously reported baseline differences between patients with SAD and controls, and in regions where bright light induced changes in rCBF), was compared between the baseline and postlight, and between patients and controls using two way repeated measures ANOVAs.
Results: After bright light treatment mood improved in patients and was unchanged in controls. Global cerebral blood flow did not differ between baseline, on light and postlight conditions. A significant effect of condition but not of diagnosis or interaction, was revealed for the asymmetry index in the AI/VLPFC ($p<0.01$), but not other regions. After light treatment, in both patients and controls, while the rCBF increased in the AI/VLPFC bilaterally, rCBF increased on the left side more as compared to the right side ($p<0.01$).
Conclusion: Given the partial antidepressant effect of one session of light treatment in depressed individuals, the shift from the right to left in the AI-VLPFC is consistent with the current understanding of lateralization of the prefrontal cortex in emotional regulation and dysregulation. The effects of bright light treatment on brain laterality are independent of mood changes.

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Disrupting Life Events are Associated with Interrupted Sleep in Depressed Individuals but Not in Normal Controls

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Introduction: The influence of life events on sleep and activity rhythms has not been explored in individuals with unipolar depression, despite research indicating that both disrupted sleep and life events are risk factors for depression. We hypothesized that depressed individuals who experienced at least one social rhythm disruption (SRD) event would have more disrupted sleep and circadian rhythms as compared to normal controls who experienced at least one SRD event.
Methods: Thirty-nine depressed outpatients and 39 age (± 5 years) and gender-matched never-depressed controls (M age = 43.73 years; SD = 12.88) participated in the study. Over the course of two weeks, participants (1) completed retrospective, life events interviews assessing the frequency of events that occurred in the previous 4 months, and (2) wore Actillumes (Ambulatory Monitoring, Inc., Ardsley, New York), wrist-mounted monitors that record motor activity in one-minute epochs. All life events were scored according to the Life Events and Difficulties Schedule (LEDS), Social Rhythm Disruption Criteria. An event received a high SRD rating if it contributed to an acute sleep disruption, substantial change in routine likely to promote sleep disruption, or a change in the sleep/wake routine. Sleep/wake and cosinor activity variables were estimated from average activity counts using an automated sleep-wake scoring algorithm in the ACTION4 software package (Ambulatory Monitoring, Inc., Ardsley, New York). Participants wore the Actillume a mean of 4.91 nights (SD = 1.57) and 3.30 days (SD = 1.87).
Results: Hierarchical linear regression analyses yielded a statistically significant SRD events x group interaction when predicting the activity mesor, $F\Delta(3, 40) = 5.24$, $p < .05$. Greater differences in mesor level emerged between groups in the no SRD event condition. Depressed individuals had a lower mesor (i.e., lower midpoint of the activity rhythm) in the absence of an SRD event, as compared to normal controls and depressed individuals with an SRD event. Significant interactions for SRD events x group were also found when predicting sleep percent, $F\Delta (3, 73) = 7.41$, $p < .01$, and wake time after sleep onset, $F\Delta (3, 73) = 5.17$, $p < .05$. These interactions indicated that the presence of an SRD event was associated with worse sleep continuity in depressed individuals than in normal controls.
Conclusion: The presence of a social rhythm disruption life event in the previous four months correlated with disrupted sleep continuity in depressed individuals but not in normal controls. These findings lend support to the social rhythm model of depression. Individuals with depression may have a biological vulnerability to stressful life events that is expressed as disrupted sleep and rhythms. This vulnerability may be reflected in a lower activity mesor level. To our knowledge, this is the first study to date testing the social rhythm hypothesis of depression using objective sleep measures and life event ratings.

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The Relationship Between Habitual Behaviors and Depression is Partially Mediated by Light

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Introduction: Researchers have hypothesized that habitual behaviors are social zeitgebers for the circadian clock and some studies have, in fact, found support for a direct relationship between habitual behaviors and circadian rhythms. However, no studies to date have examined the relationship between habitual behaviors and light, the strongest zeitgeber. Depression is an ideal model to explore this relationship because of documented disruptions in circadian biological activity, sleep, and social rhythms (or patterns of habitual behaviors). We hypothesized that light exposure would mediate the relationship between habitual behaviors and mood. Thus, individuals with irregular social rhythms and fewer habitual activities would have lower exposure to light, and lower light exposure would be directly associated with an increased likelihood of depression.
Methods: Thirty-nine depressed outpatients and 39 age (± 5 years) and gender-matched never-depressed controls (M age = 43.73 years; SD = 12.88) participated. Over the course of two weeks, participants completed the Social Rhythm Metric, a prospective, self-report, measure, which was used to compute indices measuring (a) the regularity of habitual behaviors in an individual's life (i.e., social rhythms) and (b) the overall number of habitual behaviors in an individual's life. Participants wore Actillumes (wrist-mounted monitors that record motor activity and light exposure in one-minute epochs; Ambulatory Monitoring, Inc., Ardsley, New York) a mean of 4.91 nights (SD = 1.57) and 3.30 days (SD = 1.87). Actillume data were recorded and analyzed on a logarithmic scale. Mean daily out-of-bed lux was computed as a summary variable for use in the analyses.
Results: Linear and logistic regression techniques were used to test for mediation with the MacKinnon approach. Irregular social rhythms and a lower number of habitual behaviors were each directly associated with (a) an increased likelihood of depression and (b) decreased exposure to light. Statistically significant partial mediation effects emerged for the regularity of social rhythms ($z' = -1.45$, $p < .02$) and the number of habitual behaviors ($z' = -1.44$, $p < .02$). Each of these variables was indirectly associated with an increased likelihood of depression via decreased light exposure. Controlling for light, the direct effects of irregular social rhythms ($\beta = -1.25$, $p < .01$) and fewer habitual behaviors ($\beta = -6.68$, $p = .07$) remained.
Conclusion: These findings are somewhat consistent with our hypothesis. Light exposure partially mediated the relationship between habitual behaviors and mood. Individuals with irregular social rhythms and fewer habitual behaviors had lower exposure to light; lower light exposure was associated with an increase in the likelihood of depression. Irregular social rhythms and fewer habitual behaviors were also directly associated with an increased likelihood of depression when controlling for light. Thus, these findings do not preclude the possibility that the overall number and regularity of habitual behaviors have a role in the direct entrainment of circadian rhythms. Future studies are needed to determine whether irregular social rhythms, a lower number of habitual behaviors, and low light exposure precede the development of depression, thereby indicating risk factors in the development of the disorder.

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Evaluation Of Subjective Fatigue Versus Sleepiness As A Consequence Of Various Sleep Disorders

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Introduction: Chronic high fatigue is a very common complaint in primary healthcare setting. In sleep-disordered patients, it is generally equated with excessive sleepiness and thus less emphasized and even ignored as an independent symptom. Distinguishing between fatigue and sleepiness may be important as the etiology and treatment of these two symptoms may differ. The possibility of high fatigue being a key complaint in patients with a primary sleep disorder needs to be investigated. The objectives of this investigation included evaluation of subjective fatigue and sleepiness in sleep-disordered patients and how these symptoms relate to alertness, depressive symptoms and illness intrusiveness.
Methods: In a prospective observational study, 283 sleep-disordered patients referred to a hospital based sleep laboratory for various indications over a one-year period were evaluated vis-à-vis fatigue and sleepiness. All patients completed six subjective questionnaires, attended a clinical interview and underwent overnight polysomnography for objective sleep measurements. Selection of the subjects from the total subject pool was based on recruiting patients who were free from a prior diagnosis of a condition known to cause fatigue and/or sleepiness. Patients on drugs that may cause fatigue or sleepiness were also excluded. The subjective questionnaires completed by the subjects included the Fatigue Severity Scale (FSS), the Fatigue Assessment Instrument (FAI), the Epworth Sleepiness Scale (ESS), the Toronto Hospital Alertness Test (THAT), the Illness Intrusiveness Rating Scale (IIRS) and the Center for Epidemiologic Studies-Depression (CES-D) Scale.
Results: Only 4% of the sample (N=283) were referred to the sleep clinic due to excessive fatigue compared with 17% for excessive daytime sleepiness. However, during assessment, 64% reported of high subjective fatigue without overlap of sleepiness and only 4% reported of excessive sleepiness without overlap of fatigue. Pearson's correlation analysis indicated a very weak association ($r=.18$) between the symptoms of fatigue and sleepiness. We also found negative correlation between subjective alertness versus fatigue and sleepiness in the sample. ANOVA testing showed strong association between highly fatigued sleep-disordered patients and depressive symptoms ($p<0.001$) and illness intrusiveness ($p<0.001$).
Conclusion: The findings support the notion that subjective fatigue and sleepiness can be independent manifestations of sleep disorders. Furthermore, highly fatigued individuals with sleep disorders are more vulnerable to additional negative consequences due to possible interplay between amplified fatigue and psychological distress.

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An Evaluation of Sleep-Related Distress as a Predictor of Depression

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Introduction: When evaluating sleep disturbance, clinicians and researchers often focus exclusively on measures of sleep quantity (e.g., total sleep time), abnormal sleep parameters within the sleep period (e.g., increased sleep onset latency), or the presence of an insomnia complaint (e.g., early morning awakenings - EMAs), with little consideration

of the assessment of distress. The following study investigated whether sleep-related distress on the Symptom Checklist (SCL-90-R) was a useful addendum to the sleep items of the Hamilton Rating Scale for Depression (HRSD) and the Beck Depression Inventory (BDI-II) in predicting depression levels.
Methods: Patients (M = 37.36 years old, SD = 10.64) presenting with depression (N = 78) at the Centre for Addiction and Mental Health (CAMH) were assessed pre-treatment with the BDI-II, SCL-90, and the HRSD. Sleep items were removed from the 17-item HRSD (#6-8) to assess the level of depression. Items of the SCL-90 were used to assess sleep-related distress (#44 - sleep onset distress; #64 - EMA distress; #66 - sleep maintenance distress). Item 16 of the BDI-II was used to assess sleep quantity (e.g., an increase/decrease in sleeping relative to usual sleep quantities). The HRSD items were used as an indication of insomnia (#6 - sleep onset insomnia; #7 - sleep maintenance insomnia; #8 - EMA).
Results: Multiple regression analyses revealed that sleep distress ($R2 = .22$, $F(5,65) = 3.67$, $p = .006$), sleep quantity ($R2 = .16$, $F(2,68) = 6.39$, $p = .003$), and insomnia complaint ($R2 = .25$, $F(8,62) = 2.60$, $p = .016$) significantly predicted depression. Regression analyses also revealed that sleep-related distress did not predict depression after controlling for sleep quantity (R2 change= .06, $F(3,65) = 1.71$, $p = .243$), nor did it predict depression after controlling for an insomnia complaint (R2 change = .06, $F(3,66) = 1.43$, $p = .175$). The only measure significantly predicting depression after controlling for the other measures was sleep quantity. A stepwise multiple regression analysis was conducted to evaluate how well pre-treatment sleep items predicted levels of depression. There were two variables entered into the model: the report of sleeping more (BDI) significantly predicted depression ($R2 = .86$, $F(1,69) = 6.47$, $p = .013$), and the report of EMAs (HRSD) predicted depression even after controlling for the amount of variance attributable to sleeping more (R2 change = .098, $F(1,68) = 8.18$, $p = .006$).
Conclusion: Sleep-related distress did not significantly add to the prediction of depression. Levels of depression on the HRSD were best predicted by using reports of sleeping more (BDI-II) and EMAs (HRSD). This finding is consistent with the sleep literature, as depression is often accompanied by complaints of early morning awakenings and increased time spent in bed. In addition, the BDI-II was a useful predictor of depression even after controlling for the variance attributable to an insomnia complaint and sleep-related distress. Future investigations should replicate these results using validated measures of sleep distress, and evaluate sleep-related distress in other populations, e.g., insomnia or anxiety populations.

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Do Anxious Patients Complain More Of Insomnia Than Anxiety To General Practitioners?

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Introduction: Patients with generalized anxiety disorder (GAD) are known to be high health-care users, yet seldom complain about overwhelming worry, a hallmark feature of GAD. In outpatient medical clinics, it appears that these patients mostly present complaints regarding the somatic symptoms of the disorder (which include insomnia) rather than anxiety per se, making GAD difficult to identify. The objectives of this study were to examine if more individuals meeting GAD criteria presented complaints of insomnia than complaints of anxiety to general practitioners and if they presented higher insomnia severity than those not meeting GAD criteria.
Methods: A total of 1110 consecutive individuals above 16 years of age [68% women; mean age: 42 years (SD = 15.7)] seeking health care in outpatient medical clinics participated in this study. They completed a survey aimed at assessing frequency and health-care utilization behaviors of individuals who screened positive for GAD. The Worry and Anxiety Questionnaire (Dugas et al., 1995), an 11-item questionnaire measuring the presence and severity of GAD symptoms according to DSM-IV diagnostic criteria, was used to screen for the presence of GAD. Presence and severity of insomnia symptoms were assessed using the Insomnia Severity Index (Morin, 1993), a 7-item questionnaire measuring insomnia severity, dissatisfaction with sleep, interference of insomnia with daily functioning, and worry about the consequences of poor sleep.
Results: A total of 219 (19%) individuals screened positive for GAD on the Worry and Anxiety Questionnaire. These individuals reported consulting a general practitioner significantly more often, with an average of 5.4 (SD = 5.9) consultations annually compared to 3.4 (SD = 3.8) for the rest of the sample, $p < 0.01$. Regarding insomnia versus anxiety complaints in the past year, 18.6% of individuals with a positive GAD screen reported having consulted a general practitioner specifically for insomnia, 5.1% specifically for anxiety, 22.9% for both problems, and 52.9% reported not having consulted for either one. Significantly more individuals reported having consulted for insomnia than for anxiety, 95% CI of the difference: [4.7-21.1], $p < 0.05$. Individuals with a positive GAD screen also reported more severe insomnia symptoms (M = 13.3, SD = 5.5 compared to M = 6.7, SD = 4.9, $p < 0.0001$).
Conclusion: Many outpatients suffer from anxiety and insomnia, yet these symptoms often remain unrecognized. A complaint of insomnia may in some cases indicate an underlying anxiety disorder and warrant a more in-depth investigation. Indeed, it appears that some patients with a positive GAD screen complain of insomnia more readily. However, a considerable number of patients who suffer from anxiety and insomnia do not present either complaint to general practitioner. Other indicators must be identified.

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Psychiatric Diagnoses of Patients Visiting a Sleep Disorder Clinic due to Dyssomnias

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Introduction: Several studies found that most insomnic patients visited sleep clinics were associated with psychiatric diagnoses, particularly depressive disorders. Other disorders included sleep related breathing disorders, narcolepsy, periodic limb movement disorders were also found at sleep disorders clinics. Research about the characteristics and psychiatric diagnoses of patients using sleep clinic in Asian countries was rarely seen. Under the above considerations, we analyzed the demographic and clinical characteristics of patients who visited the sleep disorder clinic and the psychiatric diagnoses among this population in Taiwan.
Methods: Several studies found that most insomnic patients visited sleep clinics were associated with psychiatric diagnoses, particularly depressive disorders. Other disorders included sleep related breathing disorders, narcolepsy, periodic limb movement disorders were also found at sleep disorders clinics. Research about the characteristics and psychiatric diagnoses of patients using sleep clinic in Asian countries was rarely seen. Under the above considerations, we analyzed the demographic and clinical characteristics of patients who visited the sleep disorder clinic and the psychiatric diagnoses among this population in Taiwan.
Results: There were 56 men and 34 women. Their age distribution was from 13 to 79 years, with a mean of 41.5 (SD 15.6). No significant dif-

ference in the age between sex.(t=-.651, d.f.=88, p=.517). Among them, 79 (87.8 %) were insomnia and 11(12.2%) were hypersomnia. Fifty-three (58.9%) subjects had psychiatric diagnoses other than sleep disorders. Subjects with insomnia had significantly higher rate of comorbidity with other psychiatric diagnosis (65.8%) than subjects with hypersomnia(9.1%). The most frequent diagnoses of insomnic patients were primary insomnia (38.0%), followed by insomnia related to mood disorders (34.3%), insomnia related to anxiety disorders (12.7%) and circadian rhythm sleep disorder(4.4%). The definite diagnoses of hypersomnia were breathing related sleep disorder(27.3%), primary hypersomnia(18.2%), and narcolepsy(18.2%).
Conclusion: The high rate of psychiatric morbidity among patients with dyssomnia emphasizes the importance of psychiatric evaluation of patients with sleep disturbance complaints.

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Sleep in Adults With High-Functioning Autism or Asperger Syndrome

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Introduction: Autism and Asperger syndrome (AS) are two related pervasive developmental disorders (PDD). Numerous studies have reported sleep disturbances in PDD, more particularly in preschoolers and school age children with autism and comorbid intellectual retardation. Fewer studies have analyzed sleep in normal IQ adults with autism or AS using polysomnography (PSG). The objective of the present study was to compare PSG patterns in adults with high-functioning autism (HFA), AS, and control participants.
Methods: Participants were 12 individuals with HFA (age: 16-27; mean: 21.3 +/- 3.9 years), 6 persons with AS (age: 17-26; mean: 22.5 +/- 3.1 years) and 18 typically developping participants (age: 15-27; mean: 21.0 +/- 4.2 years). Each participant had an IQ > 80. Sleep stages were determined according to Rechtschaffen and Kales (1968). Pathological index of Periodic movements in sleep (PLMS) was set at 10 per hour of sleep. Comparisons were made using t-tests.
Results: Compared to controls as a single group, PDD participants showed a longer sleep latency (p<.07), less percentage of deep slow wave sleep (SWS: stages 3+4) (p<.07), lower rapid eye movement density in REM sleep (p<.0002) and no differences on PLMS index. There were no significant differences between HFA and AS participants. When both clinical groups were separately compared to controls we found that participants with AS showed a significantly longer sleep latency (p<.04) and less percentage of SWS (p<.05) while HFA participants showed no significant differences with controls on sleep macrostructure. The density of rapid eye movements during REM sleep was significantly lower in AS and HFA participants compared to controls (p<.015 and p<.0005, respectively) but there were no differences between both clinical groups (p = .53). AS participants showed an increased density of rapid eye movement in stages 1+2 vs. controls and HFA participants (p<.02 and p<.05, respectively). AS participants also showed an increased PLMS index during REM sleep vs. control participants (p<.08).
Conclusion: Persons with AS show increased signs of sleep disorders, including REM sleep disturbance and thin boundaries between sleep states, compared to both HFA and control participants. We postulate that AS may represent a subset of individuals with PDD particularly at high risk for sleep disturbances. Further analyses should be done on correlations between sleep parameters and daytime functioning.

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Cortical and Cardiac Reactivity to Auditory Stimuli During Stage 2 Sleep in PTSD

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Introduction: Sleep complaints are common in people who develop Post Traumatic Stress Disorder (PTSD). PTSD-related information processing abnormalities evident during wakefulness might continue into sleep.
Methods: A group of male Vietnam veterans with and without PTSD (patients and combat-controls) were studied to examine psychophysiological responses to auditory stimuli during stage 2 NREM sleep. Three stimuli (500 ms) categories were presented in an oddball paradigm: pure tones (standard, 60% probability of occurring); trauma-related (i.e., combat sounds) and affectively neutral, environmental stimuli (20% each). The effects of stimulus presentation on cortical activity (beta-band EEG power) and heart rate (HR) were examined; the impact of the occurrence of a K-complex (KC+ and KC- trials) on these measures was also examined.
Results: At baseline, beta power did not differ between patients and controls. Post-stimulus, however, there were significant main effects of group, KC, and stimulus type (p < .038, .001, and .001, respectively). Following a stimulus, there was more beta activity in the controls than in the patients. Across both groups, beta activity was greater for KC+ trials compared to KC- trials. Both groups showed similar differences between stimulus type (from highest to lowest: neutral, tone, and trauma). Tonic heart rate was found to be (marginally) elevated in patients. There was no impact on initial HR decelerations, but analysis of the ensuing HR acceleration revealed a main effect of K-complex type (greater HR increases for K+ trials) and stimulus type (significantly higher increases to neutral stimuli).
Conclusion: Results suggest sleep-related information processing is altered in PTSD. Patients had elevated HR at baseline, although they did not differ from controls in how they reacted to the various stimuli presented during stage 2 sleep. Cortically, the patients and controls did not differ at baseline. Following a stimulus, beta activity was lower in patients relative to controls, suggesting that responses were blunted in the PTSD sample. Further research is necessary to understand information processing and arousal reactivity during sleep and waking in PTSD.

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Improvement Of Objective And Subjective Sleep Parameters Following Magnesium Treatment Of Primary Alcohol Dependent Patients During Subacute Withdrawal: An Open Pilot Study With Polysomnography

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Introduction: Sleep EEG alterations and insomnia complaints were found to persist following alcohol withdrawal in dependent patients and are considered as strong predictors of a relapse. Though disturbances of magnesium homeostasis due to alcohol consumption are well known, the relationship of magnesium metabolism and sleep disturbances has not yet been investigated in this patient group. We conducted an open pilot study to evaluate the effects of magnesium treatment on the sleep of pri-

mary alcohol dependent patients during subacute withdrawal.
Methods: Eleven out of the fourteen included patients were evaluated. Patients were free of any psychotropic medication or substances influencing sleep. Polysomnographic recordings with monitoring of periodic leg movements in sleep (PLMS) were performed for two consecutive nights 2 weeks after acute withdrawal (baseline) and 4 weeks later after treatment with 30 mmol magnesium (magnesium-L-aspartate-hydrochloride) daily over the 4 weeks treatment period.
Results: We found a significant decrease of sleep onset latency from 40.6 to 21.7 min (p = 0.03) and a significant improvement of subjective sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) from 8.1 to 5.8 (p = 0.05) during magnesium treatment. Changes of PLMS indices revealed two subgroups of patients: one with an increase of PLMS from 30.7 to 39.4 per hour of sleep (n = 4) and the other one with a decrease of PLMS from 8.9 to 2.1 per hour of sleep (p = 0.04). In the group with PLMS decrease, total sleep time also improved significantly (from 371 to 423 min, p = 0.04).
Conclusion: Results of the study should be interpreted with caution, as no control group with placebo was investigated. Both subjective and, partly, objective parameters of sleep improved during the four-week study period. PLMS improved only in a subset of alcohol dependent patients. Further research is needed to clarify the relationship of magnesium metabolism and sleep alterations.

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Morning-evening Differences in Relative Regional Glucose Metabolism During Wakefulness in Patients with Major Depression
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Introduction: We have previously used found that healthy adults show variation in relative regional brain glucose metabolism (RBGM) according to time of day, using 18F-FDG positron emission tomography (PET). RBGM is higher in brainstem and hypothalamic arousal centers in the evening compared to morning. Patients with major depressive disorder (MDD) often present with prominent diurnal variation in mood and alertness. The aim of this study was to investigate whether patients with MDD would have a different pattern of diurnal variation in RBGM during wakefulness compared to healthy adults.
Methods: Subjects were 12 adults with MDD (10F, 2M, mean age 37 years) who had no other significant sleep or medical disorders, and were not taking any medications affecting sleep or wakefulness. The first PET scan was conducted during wakefulness 3-4 hours following sleep, and the second was conducted during wakefulness at subjects' usual bedtime. Each PET scan used 4-6 mCi of [18F]-2-fluoro-2-deoxy-D-glucose (18F-FDG) to measure regional brain metabolic rate. During the 20-minute uptake period, subjects remained seated with eyes closed and no specific mental task. Continuous EEG monitoring was performed to verify wakefulness. Subjects then had imaging studies, using an HR+ ECAT scanner in 2-D mode. Six 5-minute emission frames beginning 60 minutes after injection were followed by a transmission scan. Each subject's PET scans were summed, co-registered to their high-resolution MRI scan, transformed into Tailarach coordinates, and smoothed. Absolute glucose metabolic rate for the whole brain was compared for evening and morning scans. Analyses of relative regional cerebral glucose metabolism were performed with Statistical Parametric Mapping (SPM-99), using ANCOVA to correct for global differences. Contrasts involved regions with greater RBGM in pre-sleep compared to a.m. scans and those with greater RBGM in a.m. compared to pre-sleep scans. We also examined RBGM in a priori regions of interest in the brainstem and hypthalamus. The threshold for identifying significant differences in SPM images was a corrected cluster-level p value of <0.05, with a height threshold of 0.05.
Results: Absolute glucose metabolism was numerically higher in the morning than evening, but the difference was not significant (p<.4). RBGM was higher in the evening than morning in two large regions. The first, in the medial temporal cortex, included the hippocampus and parahippocampal gyrus. The second, in the medial frontal cortex, included the anterior cingulate gyrus. Testing in specific regions of interest showed higher evening RBGM in the posterior hypothalamus, but not in the volumes including the raphe nuclei, locus coeruleus, or pontine reticular formation. RBGM was higher in the morning versus evening in a region of the occipital lobe including the cuneus.
Conclusion: The observed pattern of evening-morning differences in RBGM was different than that observed in healthy control subjects. Specifically, patients with MDD had less evidence for activation of brainstem alerting centers in the evening, and greater evidence for hippocampal and frontal midline activation. This pattern may be related to subtle alterations in circadian mood and alerting signals in MDD.

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The Effect of Tiagabine on Sleep in Patients with Posttraumatic Stress Disorder
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Introduction: Posttraumatic stress disorder (PTSD) is characterized by persistent and intrusive recollections of a traumatic event, avoidance of associated stimuli, and hyperarousal. Symptoms associated with hyperarousal in patients with PTSD include difficulty falling/staying asleep and distressing dreams. Tiagabine, a selective GABA reuptake inhibitor (SGRI), has been shown to have sleep-consolidating effects in elderly volunteers. One aim of the present study was to evaluate the effect of tiagabine on sleep in patients with PTSD.
Methods: This 24-week study in patients with PTSD (n=29) was conducted in 2 phases. The first phase was a 12-week open-label phase, in which tiagabine was initiated at 4 mg/day (2 mg BID) and increased to a maximum dose of 16 mg/day (8 mg BID). Subjects who responded to treatment (CGI-C≤3) were then randomly assigned to the double-blind phase with either tiagabine (n=10) or matching placebo (n=8) for 12 additional weeks. Assessments included patient-rated measures of PTSD (Davidson Trauma Scale [DTS]) and sleep quality (Pittsburgh Sleep Quality Index [PSQI]), and overall clinical condition (Clinical Global Impression of Change [CGI-C]). Safety evaluation included reporting of the emergence of adverse events and changes in vital signs and weight.
Results: 26 patients had one postbaseline assessment and were included in the LOCF analysis. Significant improvement with tiagabine therapy compared with baseline was observed on the DTS (p<0.05), including the distressing dreams and sleep problems items, with regard to both frequency and severity (p≤0.001). Similar results were also seen on the PSQI (p=0.001). Of the 18 subjects completing the open-label phase, 17 subjects were classified as responders and were randomized into the double-blind phase. Results of the double-blind phase showed no significant difference between active treatment and placebo. The most commonly reported adverse events were dizziness (n=7), dry mouth (n=5), nausea (n=4), headache (n=4), and constipation, drowsiness, and muscle-twitching (all n=3) in the open-label phase, and headache (n=4) in

the double-blind phase.
Conclusion: Tiagabine significantly improved symptoms associated with poor sleep in patients with PTSD in 12-weeks of open-label treatment, and was generally well tolerated. Tiagabine may have a role in the treatment and management of patients with PTSD.

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Sleep and Dreams in Patients with Anxiety Disorders: Effects of a Cognitive-Behavioral Treatment

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Introduction: Sleep and dreams disorders are a prominent feature of anxiety disorders, including subjective and objective signs of insomnia. The aim of this research was to measure characteristics of sleep and dreams in patients with anxiety disorders before and after a behavioral-cognitive therapy program.
Methods: Eight persons (5 men, 3 women; age = 23 to 59 years) diagnosed with "Social Phobia" (n=4) or with "Panic Disorder with Agoraphobia" (n=4) and 12 control participants (7 men, 5 women; age = 27 to59 years) completed the study. Subjective quality of sleep, dreams and waking were evaluated from 1 (very bad) to 10 (very good) using questionnaires filled before, during, immediately after, and 3 months after a 12-week behavioral-cognitive therapy program. Various dimensions of anxiety such as anxiety itself, shyness and physical symptoms were evaluated in the same manner (1=light, 10=serious). Control participants followed the same time interval to fill the questionnaires. Comparisons were made using 2 (Groups) X 4 (Moments) ANOVAs for repeated measures.
Results: The two groups of patients did not differ on any of the measures so their results were pooled together. Levels of general anxiety, shyness, and physical symptoms significantly decreased from baseline to the end of treatment and remained significantly lower than baseline at the 3-month follow-up. Subjective quality of sleep and waking were significantly lower than controls at baseline(6.25 vs. 8.6 and 5.5 vs. 8.5, respectively); measures improved to control levels at week 6 of treatment and were still high at follow-up. Number of dreams recalled per night and dream pleasantness increased in both groups with time, but groups were not different from each other.
Conclusion: Successful treatment of anxiety using a 12-week behavioral-cognitive therapy program is accompanied by significant and lasting improvements of waking and sleep. Number and general quality of dreams equally improved in patients and controls; content analysis remains to be performed.

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Cocaine Users Differ From Normals On Cognitive Tasks Which Show Declining Performance During Drug Abstinence

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Introduction: We previously showed that cognitive performance in chronic cocaine users declines during abstinence relative to binge in parallel with declining sleep quality over this same period. We compare performance on these same tasks between an expanded sample of cocaine users and age and sex-matched normals.
Methods: Ten non-treatment-seeking chronic cocaine users were studied as inpatients in clinical research units at Yale (5 subjects) and Columbia (5 subjects). Subjects were 8 males and 2 females of mean age 38 (range 24-47) with DSM IV diagnoses of Cocaine Dependence but no other Axis I disorders or medical illness. Subjects participated in a 22-23 day inpatient protocol with 3 days cocaine self-administration ("Binge" phase) on Days 4-6 (8 "early bingers") or Days 18-20 (2 "late bingers"). This was followed by (early bingers) or preceded by (late bingers) a 2-week period of drug abstinence ("Abstinence"). During the 3-day binge, subjects consumed NIDA-supplied cocaine, twice daily in smoked form (Columbia) or once daily intravenously via patient-controlled analgesia pumps (Yale). Subjects completed a multiply repeatable cognitive battery (CDR battery, CDR, Ltd.) twice (Columbia) or once (Yale) daily. Tasks included simple reaction time (SRT), choice reaction time (CRT), digit vigilance (DV), numeric (NWM) and spatial working memory (SWM), and delayed word recognition (DR). Mean performance on these tasks were computed for Binge (Days 4-6: early bingers or 18-20: late bingers) and late Abstinence phases (Days 19-21: early bingers or Days 13-15: late bingers). Performance values of 10 clinical trial subjects, age and sex matched to each individual cocaine subject, were obtained following 4 practice sessions. Mean Binge and Late Abstinence test scores for the 10 cocaine users were compared to those of the 10 matched norms using Bonferroni corrected unpaired t-tests.
Results: Cocaine users showed significantly longer reaction time (RT) than normals for SRT during Binge (p=.004) with a trend during Abstinence (p=.045). Cocaine users had significantly longer CRT RT than normals during Abstinence (p=.016) with similar trends for CRT RT during Binge (p=.036) and for DV RT during Abstinence (p=.04). DV accuracy was significantly greater for normals than cocaine users during Abstinence (p=.009) but not Binge. Cocaine users showed significantly poorer DR accuracy (sensitivity index) than normals during Abstinence (p=.0003) with a similar trend during binge (p=.028). No differences between normals and cocaine users were seen for CRT, NWM, or SPM accuracy.
Conclusion: We previously showed that RT on SRT, CRT and DV as well as DR accuracy significantly declined with time from Binge to Abstinence and across the Abstinence phase alone. This was not consistently seen for CRT, DV, SPM, or NWM accuracy. The current finding that similar deficits differentiate cocaine users from normals suggests that vigilance RT and recognition memory are selectively impaired in cocaine users, especially during Abstinence. Previously reported sleep quality declines seen in cocaine users during Abstinence may contribute to cognitive deficits.

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Does Residual Insomnia Predict Depressive Relapse and Recurrence in Cognitive Therapy Responders?

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Introduction: Sleep excesses and deficits are cardinal features of mood disorders (DSM-IV; American Psychiatric Association, 1994). Further, the majority of people with insomnia also endorse depressive symptoms (Taylor, Lichstein, Durrence, Riedel, & Bush, 2003). However, the

extent to which there may be a causal link between the two disorders is unknown. Longitudinal studies, such as the randomized clinical trial below, allow an opportunity to test hypotheses regarding the influence of residual insomnia in predicting depressive relapse and recurrence.
Methods: Eligible patients (N=156) with recurrent nonpsychotic unipolar Major Depressive Disorder (MDD), with clear inter-episode recovery, entered 20 sessions of acute phase cognitive therapy (A-CT) spanning 12-14 weeks. Responders to A-CT [N=84; defined by no MDD and a score of ≥ 9 on the 17-item Hamilton Rating Scale for Depression (HRSD)] were randomized to a clinical trial comparing 8 months (10 sessions) of continuation phase cognitive therapy (C-CT; n=41) versus control (evaluation without C-CT; n=43). After C-CT was discontinued, follow-up lasted an additional 16 months (i.e., two years after A-CT). Primary results showed that C-CT reduced relapse and recurrence significantly more than the control, in individuals with significant risk factors (Jarrett, Kraft, Doyle, Foster, Eaves, & Silver, 2001). In the current analysis, we tested the hypothesis that residual insomnia predicts relapse and recurrence.
Results: The responders [23 men and 61 women; 24-64 years of age (M = 42.7, SD = 10.4)], who were predominately Caucasian (90.5%), reported significant sleep difficulties before and after A-CT. Specifically, at pre-treatment, the five most frequently recorded symptoms on the HRSD, were Psychic Anxiety (70.2%), Fatigue (65.5%), Psychic Retardation (56%), Middle Insomnia (42.9%), and Onset Insomnia (40.5%). In addition, 21.4% of patients also complained of Late Insomnia (i.e., waking 1-3 hours before usual wake time and unable to return to sleep). At post A-CT the four most frequently rated symptoms were Middle Insomnia (14.3%), Decreased Libido (13.1%), Late Insomnia (9.5%), and Early Insomnia (6%). A hierarchical Cox regression analysis was performed, with time to relapse or recurrence (i.e., MDD) as the dependent variable and with condition (i.e., C-CT vs. control) entered as an independent variable and then the four residual symptoms listed above entered in a backward stepwise procedure as independent variables. The final model with condition, Early Insomnia, and Late Insomnia, was significant at a trend level, $\chi 2$ (3, N = 84) = 7.08, p = .068. Further, only late insomnia was a significant predictor of relapse or recurrence over the full two years of follow-up (Odds Ratio = 3.43: 95% CI= 1.24-9.62, p = .019).
Conclusion: These data suggest that insomnia is clearly one of the most prominent complaints of people with recurrent MDD, and that it is a significant concern even in some patients who respond to A-CT for depression. Further, residual Late Insomnia tended to predict depressive relapse and recurrence over the full two year follow-up. These findings suggest that treating residual late insomnia may reduce the risk of relapse and recurrence.

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Heart Rate Variability During Sleep in Recovering Alcoholics and Controls

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Introduction: Clinical populations with disturbed sleep show signs of autonomic dysregulation as compared to healthy controls. It is unknown whether alcoholics, who evidence poor sleep continuity and diminished slow wave sleep also show alterations in autonomic function. In this study we examined heart rate variability (HRV) during a full night of sleep in controls and recovering alcoholics. HRV is a measure of cyclic variations of heart beat-to-beat intervals, and is increasingly used as a noninvasive tool for assessment of autonomic cardiovascular control.
Methods: Polysomnographic data were collected for male recovering (abstinent between 2-12 weeks) alcoholics (n=8) and healthy control males (n=15). Regarding age, alcoholics (36.7 yrs +/- 2.6) were not significantly different from controls (35.4 yrs +/- 1.7). Both groups participated in a 3-night stay at the UCLA General Clinical Research Center. Subjects kept a regular sleep schedule prior to admission into the study of about 2300 to 700. This schedule was adhered to during the first 2 nights. On night 3, lights out was at 2300 and subjects were allowed to sleep ad libitum in order to obtain a more accurate representation of a regular night of sleep. During this night, HRV was recorded and later analyzed utilizing autoregressive spectral analytic techniques in accordance with recommended guidelines to generate estimates of parasympathetic and sympathetic function. Data were averaged through the course of the night for each subject.
Results: HRV analyses indicated that low frequency power/high frequency power (LFP/HFP) ratio was significantly higher in alcoholics (1.6 +/- 0.2) as compared with controls (0.9 +/- 0.1), $t = -2.4$, $p < 0.05$. Furthermore, normalized values of low frequency power (LFPnorm) were significantly higher in alcoholics (79.9 +/- 3.2) than in controls (70.2 +/- 2.9), $t = -2.1$, $p < 0.05$. Conversely, normalized values for high frequency power (HFPnorm) were significantly lower in alcoholics (18.0 +/- 2.7) than in controls (27.3 +/- 2.6), $t = 2.3$, $p < 0.05$.
Conclusion: During sleep, decreased parasympathetic activity was noted within the alcoholics as suggested by decreased HFPnorm values. In addition, alcohol dependence was associated with elevated LFP/HFP ratio and increased LFPnorm suggesting greater sympathetic dominance. Recent longitudinal studies have found that autonomic dysregulation indicated by diminished HRV is related to greater risk of development of cardiovascular disease. Findings from the current study suggest that autonomic cardiovascular control during sleep is dysregulated in alcoholics and this dysregulation may possibly play a role in cardiovascular disease risk.

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Functional Neuroanatomical Correlates Of Poor Sleep Quality In Depression

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Introduction: Poor sleep quality characterizes depression. Self-reported sleep disturbances often precede the onset of depressive episode or depression recurrence, and predict treatment response. Clarifying the functional neuroanatomical underpinnings of self-reported sleep quality in depression may provide new insights into the neurobiology of depression and of treatment response. The goal of the present study was to investigate the relationship between the sleep quality and relative glucose metabolism during presleep wakefulness in a sample of 12 depressed patients.
Methods: Archival data from 12 medication-free depressed subjects (M age = 37.3, SD = 11.5) were used for investigating the correlation between relative cerebral metabolic rate of glucose (rCMRglc) during NREM sleep and poor sleep quality, as determined by global scores on the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). High global PSQI scores indicate poor sleep quality. All underwent polysomnography and [18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) positron emission tomography (PET) scans during wakefulness, at their habitual bedtime. Regression analyses were conducted with Statistical Parametric Mapping (SPM-99). Global PSQI scores were entered as the predictor variable, and rCMRglc was during presleep wakefulness was

entered as the dependent variable (after correcting for the effects of inter-subject differences in global metabolism). Statistical significance was set at p< .05 after corrections for multiple comparisons.
Results: Mean global PSQI score was 10.1 (SD = 3.3), indicating poor sleep quality in this sample. During wakefulness and NREM sleep, high PSQI scores (i.e., poor sleep quality) were significantly correlated with reduced rCMRglc in two areas. The first area included the midline medial and lateral prefrontal cortex. The second area included the right transversal and superior temporal gyri, insula, and parahippocampal gyrus.
Conclusion: Poor sleep quality is associated with reduced rCMRglc during wakefulness in frontal and temporal frontal regions. The significant correlation between poor sleep quality and reduced rCMRglc in the medial and prefrontal cortex raises the possibility that the relationship between poor sleep quality and depression onset or recurrence may be attributable to frontal deficits. Poor sleep quality was also correlated with reduced rCMRglc in right temporal and parahippocampal regions. Functional anomalies in temporal regions have been associated with depression severity, but further research is necessary to clarify the functional significance of this finding in relation to sleep.

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Sleep and Dream Habits in Middle-Aged, Non Hospitalized Patients with Chronic Schizophrenia: Effects of Neuroleptics and Adjuvant Pharmacotherapy

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Introduction: Individuals with schizophrenia complain of sleep and dream disorders even when stabilized with neuroleptics. The aim of the present study was to evaluate the relationship between pharmacotherapy and sleep/dream habits in a large sample of patients.
Methods: Questionnaires on sleep and dreams habits (Chouinard et al., APSS 2002) were completed by 150 outpatients with schizophrenia (67% men, 33% women, mean age 39.8 +/- 9.3). Information on pharmacotherapy was retrieved from hospital files and direct interviews for all but 14 patients; an additional three patients was found not taking any neuroleptics at the time of the study and 26 were taking both typical and atypical neuroleptics. T-tests were used to compare the following subgroups of patients: 1-Typical (n=52, mean age: 42.4 +/- 9.6) vs. Atypical neuroleptics (n=55, mean age: 38.9 +/- 9.6), 2-Adjuvant antiparkinsonian drugs (n=68, mean age: 39.4 +/- 8.8) vs. none (n=67, mean age: 41.4 +/- 9.8), 3- Adjuvant benzodiazepines (n=56, mean age: 40.8 +/- 9.6) vs. none (n=80, mean age: 39.4 +/- 9.1), 4- Adjuvant antidepressants (n=30, mean age: 38.0 +/- 9.6) vs. none (n=106, mean age: 40.6 +/- 9.1).
Results: Compared to atypical neuroleptics, typical neuroleptics was associated with less time in bed (9:10 +/- 2:35 vs. 10:15 +/- 1:30; p < .01), earlier morning time out of bed on week days (clock time: 7:52 +/- 2:41 vs. 8:52 +/- 2:13; p<.04) and week-ends (clock time: 8:30 +/- 2:43 vs. 9:46 +/- 2:00; p < .008) and higher nap frequencies both on week days (60% vs. 40%) and week-ends (59% vs. 35%). There were no differences on dream characteristics. Adjuvant treatment with antiparkinsonian drugs was associated with shorter sleep latency, (0:28+/-0:29 vs. 0:44+/-0:41; p<.01), lower frequency of vivid dreams (on a 1(never) to 5(always) scale: 2.6 +/- 1.2 vs. 3.1 +/- 1.3; p < .04), and lower frequency of apprehension (on a 1(never) to 5(always) scale: 2.5 +/- 1.1 vs. 3.0 +/- 1.1; p < .04). Adjuvant treatment with antidepressants was associated with longer wake time after sleep onset (WASO) (0:22 +/- 0:49 vs. 0:09+/-0:18; p<.03), lower rates of sleep satisfaction (60% vs. 79%), and higher dream recall rates (on a 1(no memory) to 4(remember easily) scale: 3.1 +/- 0.9 vs. 2.7 +/- 1.1; p < .04). Adjuvant treatment with benzodiazepines was associated with lower frequencies of joyful emotions (on a 1(never) to 5(always) scale: 2.5 +/- 1.0 vs. 3.1 +/- 1.1; p < .001) and increased frequencies of bad dreams (29/years vs. 12/years; p<.01) and nightmares (3.5/ year vs. 1/year; p < .04).
Conclusion: Complaints of poor sleep is more frequently associated to typical than atypical neuroleptics. Patients with adjuvant antiparkinsonian treatments report a better sleep compared to their antiparkinsonian-free counterparts. Patients on adjuvant treatment with antidepressants report more signs of disturbed sleep as well as remembering more frequently having dreamt. Adjuvant treatment with benzodiazepines is associated with dream disorders. This suggests that pharmacotherapy of schizophrenia acts along a sleep-dream continuum but comorbid psychopathology should be used as a covariant before concluding any further.

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Development of Brief Surveys to Assess Restorative Sleep and Daytime Consequences of Sleep

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Introduction: Non-restorative sleep is a primary insomnia symptom in the DSM-IV; however, no self-administered questionnaires have been developed to measure this important concept. Such a tool would be helpful in screening patients in the primary care setting and in assessing patient reported changes in restorative aspects of sleep during pharmacological treatment. This work seeks to identify the relevant domains of restorative sleep using a combination of expert opinion, literature reviews, and focus groups.
Methods: Two focus groups with people experiencing insomnia symptoms and 1 focus group with people not experiencing insomnia symptoms were conducted at UCLA during the first half of 2003. Items designed to assess restorative sleep were then drafted and cognitive interviews conducted to assess the extent to which items were understood and to revise items as needed.
Results: A total of 24 (8 males, 16 females; 19 white) individuals were included in the three focus groups. The modal age category selected by the participants was 45-54 (n = 6). Focus group participants indicated that a good night sleep was characterized by feeling rested and energetic the next day. Most participants agreed that after a good night's sleep they feel physically better and healthier, their mind is clear and they feel refreshed. They reported a sense of vitality and alertness during the day coming from good sleep. Participants felt they were more functional and could get through a heavy schedule when they had slept well the night before. The focus group input, literature review, and expert input was used to construct two survey instruments. The first is a 9-item measure of the restorative benefits of sleep, the Restorative Sleep Questionnaire (RSQ). The RSQ is designed to be completed daily at home or at a sleep center about 30 minutes after arising and starting the day. The 9 items assess the extent to which the subject feels tired, sleepy, in a good mood, rested, refreshed or restored, ready to start the day, energetic, mentally alert, or grouchy. The time the person gets up and when they complete the RSQ are also asked. The second instrument, the Daytime Consequences of Sleep Questionnaire (DCSQ), is a 10-item measure focusing on the number of days in the last week that the persons experienced a variety of negative consequences of poor sleep.
Conclusion: Restorative and refreshing sleep were described similarly by those with and with out insomnia symptoms. Further work is needed to assess the psychometric properties of the RSQ and DCSQ and to evaluate how sensitive these measures are to sleep disorders and the extent to which they distinguish between different pharmacological treatments.

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The Effect of Test Environment on the MSLT

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Introduction: A number of recent studies have shown that the MSLT is sensitive to arousal. For example, sleep latency has been shown to be significantly longer when music was being played in the room, after exposure to bright light, and in both normal subjects and insomnia patients after they had taken a 5-minute walk. It was hypothesized that MSLT would be longer when Ss were asked to leave the bedroom area except for naps as compared to remaining in the bedroom area during the testing day.
Methods: Forty adult Ss were scheduled for an MSLT after a night of sleep in the lab. Twenty-nine Ss had a "normal" MSLT. During this day, Ss primarily remained in their bedroom and sat at a desk to work at a computer or watch TV. The second group (Out-of-Room), N=11, were not allowed to remain in the bedroom except for naps. They typically spent the day in the break room where they had increased light exposure (normal window) and social interaction with other Ss.
Results: There were no significant differences in the nocturnal sleep parameters between the groups. In the ANOVA for the MSLT, there was a significant main effect for Group ($F1,38 = 13.3$, $p < .01$) and a significant group by time interaction ($F3,114 = 3.03$, $p < .05$). Sleep latencies were longer for the Out-of-Room group for all four naps but the difference was significant for only the first 3 naps of the day. The mean sleep latency for the day was 7.8 (sd 4.8) and 12.7 (sd 5.9) for the in-room and Out-of-Room groups respectively.
Conclusion: Previous studies have shown that several types of state and trait arousal can have a significant influence on MSLT results. The current data again demonstrate that relatively trivial changes in methodology can alter MSLT results. It is recommended that standard procedures (i.e., light levels, activity, surround) be applied within and across sleep centers to increase comparability of data.

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A National Validation Study of the Sleep Disorders Inventory for Students (SDIS)

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Introduction: A conservative estimate suggests that approximately 15% of all students have a sleep disorder impacting their health or daytime functioning. However, there are no nationally validated screening instruments to facilitate the identification of students with sleep disorders. It is hypothesized that the development of the Sleep Disorders Inventory for Students (SDIS) would be one solution to this poor screening and referral process that could result in many sleep referrals from professionals in the fields of education, psychology, and medicine if implemented nation-wide. The SDIS was developed to screen children between two and 18 years of age for at least four major sleep disorders (OSAS, Narcolepsy, PLMD/RLS, and DSPS) and EDS that negatively impact student performance.
Methods: After content validation and a pilot study were conducted, a National Study was undertaken with 596 students from one school district, two psychology private practices in Florida, and four nationally known sleep clinics: Carle Regional Sleep Disorders Clinic, IL, Johns Hopkins Pediatric Sleep Centers, MD, Miami Children's Hospital, FL. and Stanford Sleep Disorders Clinic, CA. Exploratory (EFA) and confirmatory factor analysis (CFA), criterion-related validity, discriminate function analysis, internal consistency and test-retest reliability were conducted on the SDIS.
Results: The content validation committee obtained 94% agreement (content validity) on which sleep items should be retained in the SDIS. Using EFA and CFA on the National sample, a four factor structure for

the SDIS-Children's Form was confirmed (age range: 2-through-10 years). These four factors were OSAS, EDS, PLMD, and DSPS. CFA confirmed a five factor structure for the older students from 11-through-18 years (SDIS-Adolescent Form). These factors were OSAS, Narcolepsy, PLMD/RLS, DSPS, and EDS. Criterion-related validity comparing the SDIS: OSAS scale with the Polysomnography RDI Index resulted in correlations of .33 ($p < .0005$) for the Children's Form and .57 ($p < .0001$) for the Adolescent Form. The SDIS: PLMD scale compared to the PLM Index on PSG was not statistically significant because parents could not distinguish between limb movement caused by OSAS or PLMD. The SDIS: EDS scale compared to the MSLT Average Sleep Latency Index had a correlation of .85 for the Children's Form, and .32 on the Adolescent Form. When compared to sleep specialists' diagnoses, the SDIS - Children's Form had a good predictive validity of 86% and the SDIS - Adolescent Form had a high predictive validity of 96%. High internal consistency was measured for the SDIS - Children's and Adolescent Forms (.91 and .92 respectively). Internal consistency for subscales ranged from .71 to .95. Test-retest reliability indicated high reliability coefficients of .97 for the Children's Form and .86 for the Adolescent Form.
Conclusion: The SDIS is a nationally developed sleep disorders screening inventory for students with high validity, reliability, specificity, and accuracy. EFA and CFA indicated a need for two sleep inventories for students, one for children, and one for adolescents. Otherwise, younger students may be under-identified, and older students may be over-identified if the same inventory is used for all ages. Although EDS is not a sleep disorder, EDS is one of the crucial constructs on a sleep inventory because EDS indicates the negative impact that the sleep disorder has on the student's daytime functioning.

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Pattern of Use and Utility of Actigraphy in a Sleep Disorders Center

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Introduction: Actigraphy is an inexpensive, objective study that records body movements as a surrogate marker of sleep and wake times. Actigraphy has been purported to provide useful information in the diagnosis of sleep disorders including evaluation of insomnia and hypersomnia. The pattern of use and the utility of actigraphy have not been well characterized. We sought to describe how actigraphy is utilized in our sleep disorders center.
Methods: We performed a retrospective survey of all actigraphs performed over a 15 month period in our sleep disorders center. Records were reviewed for study indications, demographic information, study length, study interpretations, and the order in which the actigraphy was performed in relation to other studies of the sleep disorder evalution.
Results: During the study period, there were 4,339 clinic visits, 755 diagnostic polysomnograms, 485 CPAP titrations, and 455 split studies, while only 28 actigraphs were performed. These 28 patients (15 men) had a mean age of 44 y (range 16-83). Indications for actigraphy included insomnia in 18 (64%), evaluation of sleep pattern in 7 (25%), hypersomnia in 5 (18%), and evaluation of compliance in 1 (4%). Epworth scores had a median of 5.5 (range 1-22). Actigraphy was ordered as the first study in 11 cases, second study in 10, and third study in 7, and gathered data for an average of 13 days (range 7-16). Actigraphy showed that bedtimes varied widely (mean variation 6.17 h, range 1.0-12.7) as did wake times (mean variation 6.03 h, range 1.3-19.5). Sleep per 24 h varied widely also, minimums 1.1-8.2 h, maximums 7.5-20.1 h. Interpretations of actigraphy included poor sleep hygiene in 25 cases, sleep state misperception in 1, delayed sleep-phase syndrome in 1, and fragmented sleep in 1. Further studies were prompted in 15 cases (13 polysomnograms). When actigraphy was the first test, further tests were avoided in only four cases (14%).
Conclusion: Actigraphy commonly provides helpful information for diagnosis and management of sleep disorders and may be underutilized in our sleep center. The main indication for actigraphy was insomnia and the actigraphy data usually led to useful interpretations. The length of study time was not uniform suggesting variability in our practice patterns. Actigraphy did not frequently serve as the single definitive diagnostic test.

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Temperament and Character Inventory and Behavioral Attitudes and Search Evaluation as Assessment Tools of Personality Traits of Non-Compliant Sleep Apnea Patients

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Introduction: Personality plays an important role in the accessing of care and the acceptability of treatment recommendations. Despite this, in the field of sleep medicine, the role of personalities traits is understudied. To the best of our knowledge there are few studies specifically focused on behavioral attitudes and compliance in sleep apnea. The purpose of the present study was to evaluate personality traits in a sample of non-compliant with CPAP therapy sleep apnea patients. Personalities traits were assessed by two personality scales: The Temperament and Character Inventory (TCI; Cloninger CR, 1994) and Behavioural Attitudes and Search Evaluation test (BASE; Rotenberg V, 1996).
Methods: Two hundred seventy six patients of the Sleep Research Laboratory and satellite clinics who had previously been diagnosed with sleep apnea but subsequently refuse to go onto CPAP were asked to complete TCI and BASE tests. Replies with the completed questionnaires were received from twenty-one participant (11 males and 10 females, aged 57.5+/-12.8). Personality traits such as novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence have been assessed in the analysis. The semiprojective test BASE was used to assess different behavioral attitudes including search activity pattern, stereotyped, panic and passive behaviors. Analysis of variance using a general linear model procedure was employed to detect statistically significant differences in personalities traits. Further analysis included Tukey post hoc paired comparisons and non-parametric Mann-Whitney U-test.
Results: There were no significant gender differences detected by the BASE test. These individuals were found to have low search activity, chaotic behaviour and passive behaviour scores, with the passive behaviour scoring the lowest. Their stereotypic scores were found to be relatively high, when compared with the rest of the scores. On the TCI there were no evident gender differences regarding all of the characteristics, except for self-transcendence. Females scored significantly higher on this scale as compared with males ($p=0.04$). All patients demonstrated a combination of high harm avoidance and average scores for novelty seeking behaviour.
Conclusion: Non-compliant sleep apnea patients had low search activity scores. Surprisingly the patients scored relatively high on the novelty seeking scale measuring a similar personality trait. This implies that TCI and BASE can not be used interchangeably inasmuch they represent distinct instruments for the assessment of different behavioral domains.

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Normative Daytime Circadian Data of Driving Performance using Combined Electrophysiological Monitoring and Real-time Computerized Driving Simulation

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Introduction: Driver sleepiness is a major public health issue: the National Highway Traffic Safety Administration estimates that each year in the US, drowsy drivers cause 100,000 crashes, resulting in 1,500 fatalities and 71,000 injuries. While medicolegal aspects of this issue are relevant to physicians, no accurate standardized hospital-based diagnostic instruments exist to assess impairment due to neurocognitive impairment. Our group has developed a normative data-base of driving performance and EEG-verified cognitive functioning during simulation testing processes.
Methods: Thirty healthy adults (20M, 10F, mean age 31.7+/-11.5) with valid drivers licenses were screened for significant medical, psychiatric or sleep disorders; concomitant use of sedating or stimulating substances was disallowed. Using the York Driving Simulator, subjects performed four intentionally soporific 30-minute driving simulations at two-hour intervals (i.e. at 10:00, 12:00, 14:00, 16:00). During each session, individuals had EEG monitoring for absence episodes (AEs) — defined as intrusion of any sleep stage or alpha-/theta-EEG activity lasting more than 3 seconds but less than 30 seconds. Subjective states of sleepiness, alertness and fatigue were serially measured before each driving session via visual analogue scales. Measured performance variables included: mean lane accuracy/road position (RP), mean speed, speed deviation, mean reaction time (RT) to virtual wind gusts and off-road events (crashes). Mean values of each variable at every time of simulation were analyzed using a general linear model.
Results: Over the span of four daytime testing sessions, the following mean performance measures were obtained: Speed: 89.2km/h+/-4.1; Speed Deviation: 0.75km/h+/-0.39; RT: 1.026 sec+/-.386; RP: 29.0+/-4.16; Crash Rate: 1.34+/-1.16. On polygraphic monitoring, subjects experienced AEs with a mean frequency of 0.80 (s.d. 1.16, skewness 1.53).Circadian variation in test performance was noted with respect to RT ($F=3.1$, $p=.03$, $df=3$) and RP ($F=3.8$, $p=.01$, $df=3$), with significantly more accurate road position and quicker reaction times during the first driving session compared to subsequent trials. In terms of EEG-verified AEs, significant diurnal variation was observed: ($F=3.4$, $p=.04$, $df=3$) with a higher occurrence of absences on afternoon driving sessions. In contrast to this neurophysiological evidence, participants failed to report significant diurnal fluctuations of subjective fatigue, alertness and sleepiness.
Conclusion: This normative data of combined simulated driving performance and EEG-monitoring shows significant fluctuations in reaction time, lane accuracy and intrusion of sleep-related EEG activity. There appears to be a discrepancy between subjective and neurophysiological occurrence of attention lapses or microsleep episodes, implying that polygraphic/EEG monitoring may detect such impairments more accurately. Using a low-cost hospital based driving simulator, we will be able to use this data to compare to clinical populations of interest. Results from this database will serve as normative comparators to patients with a variety of sleep disorders and other medical conditions affecting neurobehavioural functioning, allowing a more accurate screening tool for potential crash risk by clinicians.

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The Epworth Sleepiness Scale as a Screening Tool for Sleepiness in Psychiatry

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Introduction: U.S. National Institutes of Health data show that community respondents (N=7954) with persistent hypersomnia who were not depressed and had no evidence of a psychiatric disorder at baseline had a 28.6% incidence of a new episode of a depressive disorder one year later. This compares with a 1% incidence of a new depressive episode in those who did not have persistent hypersomnia at baseline, indicating that persistent hypersomnia may signal the approach of a depressive episode. The Epworth Sleepiness Scale (ESS) is a screening tool commonly used in sleep medicine, but its use may be limited in psychiatry. This retrospective study evaluated the incidence of sleepiness using the ESS at initial visit in patients with depression and determined if there was a significant correlation between sleepiness severity and mood level.
Methods: Patients presented to the psychiatric facility between February 2001 and December 2002 with a current or previous diagnosis of major depressive disorder (single episode or recurrent). Diagnoses were clinically assessed and conducted or confirmed using the Beck Depression Inventory and patient interviews. Patients were asked to complete an ESS questionnaire during the initial visit to determine their severity of sleepiness. Total ESS scores greater than or equal to 10 were considered to be indicative of clinically significant sleepiness.
Results: Data from 161 patients with a mean age of 36.4 years were evaluated. One hundred twenty-nine patients (80%) were female and 32 (20%) were male. Eighty-eight of 161 patients (55%) had an ESS total score of <10 (mean[±SD]=5.6±2.5) at initial visit; 73 patients (45%) had an ESS ≥ 10 (mean=13.5±3.0), indicating pathological sleepiness. Ninety-two (57%) patients were taking antidepressant medication. The mean Beck Depression score for patients with an ESS total score of <10 versus ≥ 10 at initial visit was 23.3±11.3 versus 30.1±11.5 ($p=.002$), respectively. A correlation analysis of the ESS and Beck Depression Inventory Scale showed a significant causal relationship of sleepiness severity and depression symptoms ($p<.0001$).
Conclusion: Patients with depression commonly have sleepiness when presenting to a psychiatric facility. Similar to findings in other studies, patients with excessive sleepiness have significantly higher levels of depression. Since long-term excessive sleepiness/hypersomnia may trigger an emerging depressive episode, early recognition and treatment of excessive sleepiness/hypersomnia may prevent future episodes of depression. The ESS is an appropriate tool to identify pathological sleepiness and to track treatment effects in clinical psychiatry.

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Objective And Subjective Measures Of Sleepiness And Alertness Across Four Sleep Disorders

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Introduction: The literature concerning the relationship between objective and subjective sleepiness and alertness in patients with various sleep disorders is limited. Many tests have been developed (notably the Epworth Sleepiness Scale, Toronto Hospital Alert Test, ZOGIM-A, Multiple Sleep Latency Test, and Maintenance of Wakefulness Test) and studied, but analysis of the relationship of the aforementioned is limited. The present study was carried out as a continuation of a previous one and

is intended to clarify the relationship between objective and subjective measures of sleepiness and alertness and the correlation of the MSLT and MWT in four groups of sleep disordered patients viz with sleep apnea, narcolepsy, periodic leg movement in sleep, and insomnia.
Methods: In a 100-patient sample (35 patients with sleep apnea, 24 with PLMS, 19 with insomnia, and 22 with narcolepsy), two tests (MSLT and MWT) were recorded and analyzed in order to measure the objective sleepiness and alertness of the patients. Subjective sleepiness was measured by the ESS and subjective alertness by both the ZOGIM-A and THAT. In addition, the BMI and CES-D scores were also recorded and tabulated as measures of obesity and depression in this patient population.
Results: There was a very significant but weak correlation between the MSLT and MWT latencies (r= .271, p= .006) for the group as a whole. There was a significant yet weak, inverse correlation between the MSLT latencies and ESS scores (r= -.254, p= .011). There was a very significant, strong correlation between ZOGIM-A scores and MWT latencies (r= .613, p= .003) only for the group of narcoleptic patients. No significant correlation was found relating objective and subjective alertness for the group as a whole, nor sleepiness and alertness to obesity. There were very significant, strong, inverse correlations for the CES-D with the ZOGIM-A (r= -.464, p< .001) and THAT scores (r= -.560, p< .001) for the whole group, as well there were significant findings for each patient group.
Conclusion: In the evaluation of sleep-disordered patients, the subjective and objective states of impaired alertness and sleepiness did not correlate strongly, confirming these to be independent constructs of each other, as opposed to opposites of the same continuum. As the correlations between subjective and objective measures of sleepiness and alertness are weak, this suggests each tool assesses different aspects of sleepiness and alertness. The strong correlation between objective and subjective measures of alertness (MWT and ZOGIM-A) only in the group of narcoleptics suggests these tools may be more sensitive to different groups of sleep-disordered patients. Depressed patients did not subjectively feel alert, yet they did not sleep more, or fall asleep more easily.

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EEG Transient Arousal and Its Effect on Sleep Stage Complexity

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Introduction: Respiratory or movement arousals typically result in a shift from a deeper sleep stage to a lighter sleep stage or awakening. However, this same sleep stage shift is not necessarily seen for the EEG transient arousal (TA). In this study, sleep stage epochs immediately before and after an epoch containing a TA event are evaluated using a nonlinear, complexity measure to determine if there is a shift in EEG waveform complexity (correlation dimension, D2) before and after the TA event.
Methods: Sleep records for 20 subjects (13 males and 7 females), aged 25-46 who had a measured AHI ≤ 5.0, PLMS ≤ 0.2 and a TST > 300 minutes were scored for TA according to ADSA scoring rules using EEG channel C4-A1 and submental EMG. Sleep stage epochs containing TA were selected and tabulated by sleep stage: S1 (stage 1), S2 (stage 2), SWS (stages 3 and 4) and REM (rapid eye movement sleep). The complexity measure was calculated, using the tools of deterministic chaos theory, for 2 30-second epochs (one minute) prior to the 30-second epoch containing the TA (pre) and for 2 30-second epochs (one minute) immediately following the epoch containing the TA (post). A total of 44 S1 TA, 27 S2 TA, 21 SWS TA, and 26 REM TA were selected from 20 subjects and were analyzed. A one-tailed t-test for two correlated means was used to determine the significant difference between EEG waveform complexity (D2) averages for pre and post epochs within each sleep stage. The percent difference between the pre and post TA D2 values also was calculated for both NREM and REM.
Results: The S1 pre correlation dimension D2 mean was 4.60 and the post was 4.70, p = 0.004. The S2 pre was 4.22 and the post was 4.46, p = 0.012. The SWS pre was 3.58 and the post was 3.89, p = 0.008. The REM pre was 4.54 and the post was 4.55, p = 0.255. D2 values in all NREM (S1, S2 and SWS) sleep stages increased from lower complexity in the pre TA epoch to higher complexity in the post TA epochs (p < 0.05). However, the pre-post TA epoch D2 change in REM sleep was not significant (p > 0.05). SWS had the highest average pre-post difference at 11.59 followed by S2 at 10.45. Both S1 and REM had low percent difference values of 4.05 and 6.42 respectively.
Conclusion: The complexity of each sleep stage is well documented with the lower complexity indicating SWS and higher complexity for stages 1 and REM. All NREM sleep stages showed a significant increase in the complexity of the average post-TA epoch. These results suggest that TAs seen in all stages of NREM sleep are in fact related in some way to "lightening" of sleep when using a nonlinear analysis. This finding also supports the supposition that TA has the largest effect on the waveform complexity in the deeper stage of sleep. TA does not seem to alter the waveform complexity pre TA to post TA in REM sleep. This suggests that TA may play little or no role in altering REM sleep. Nonlinear correlates such as the correlation dimension should be applied to the sleep EEG as an alternative measure that can elucidate parameters that are otherwise unrecognized by traditional spectral analysis methods.

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Adherence to the Multiple Sleep Latency Test Guidelines: A Nation Wide Survey

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Introduction: Crucial decisions in the diagnosis of sleep disorders often depend on results from the MSLT. Similarly, the evaluation of therapeutic efficacy also relies on MSLT findings. While mean latency is assumed to reflect the inherent sleepiness of the patient, prior research suggests that methodological factors other than sleepiness can alter the MSLT score. To minimize these extraneous factors and maximize standardization, published guidelines exist for proper administration of the MSLT. Our study reports the extent to which sleep centers adhere to these guidelines.
Methods: A 30 item survey was mailed to all accredited sleep centers and labs listed in the 2003 APSS Directory (N=525) with instructions to answer as honestly as possible based on standard practice in the center (i.e., not simply written protocols). To assure anonymity the survey contained no information that identified the Center. At the time of this submission, a return rate of approximately 50% was achieved (258 surveys).
Results: The majority of survey items fell into two main categories of procedural and situational factors. Although recommended by the ASDA, 9% of the centers did not routinely require a nocturnal PSG prior to the MSLT. Start time for the test was generally consistent with established guidelines of 1.5 to 3.0 hours following morning waketime. Approximately 14% of the respondents obtained either respiratory or PLM recordings in addition to the standard EEG, EOG, EMG and EKG. The number of naps administered varied, with 54% of centers conducting a four-nap MSLT and 44% administering five naps. Naps were typically ended 15 minutes after sleep onset (90%), although the definition of sleep onset showed considerable variability: 83% of centers defined

sleep onset as the first epoch of any stage of sleep, while 15% defined it as the first three epochs of stage 1 or one epoch of any other stage. With respect to situational factors, caffeine consumption was prohibited in 100% of centers, but greater variability was shown in other prohibited activities: 73% resting in bed, 38% exercise, 25% walking, 7% work-related activities, 7% internet, and 6% computer games. 67% asked patients to withdraw from stimulants prior to the test, while 53% withdrew nocturnal hypnotics, 31% tricyclic antidepressants, 26% SSRIs, and 24% antihistamines. A urine drug screen prior to the MSLT was typical in 47% of the centers. Contrary to suggested guidelines, 25% of the respondents allowed patients to wear their normal bed clothes throughout the MSLT.

Conclusion: Although guidelines exist that describe the proper administration of the MSLT, our results indicate significant differences in how the test is actually conducted among accredited centers. In addition, current guidelines fail to address recent findings that identify other factors potentially affecting the MSLT score (e.g., food intake, cognitive arousal, last nap effect, respiratory-related arousals). This variability in procedure and failure to control for confounding factors may render clinical data unreliable, as well as compromise inter-center comparisons. More stringent adherence to existing guidelines appears imperative, along with the development of additional guidelines based on more recent findings.

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Observed Versus Actigraphically Estimated Daytime Sleep In Older Adults Undergoing Subacute Rehabilitation In A Nursing Home

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Introduction: Although wrist actigraphy has been validated relative to EEG and behavioral observations for the study of nighttime sleep in long-stay nursing home (NH) residents, little data are available on its validity for measuring daytime sleep in this setting. The purpose of this study was to evaluate the agreement between observed and actigraphically estimated daytime sleep in older adults participating in a larger descriptive cohort study of sleep and subacute rehabilitation in the NH setting.

Methods: 159 older adults (≥ 65 years) participating in the larger study (mean(SD) age = 81(9) years; 56% female) wore wrist actigraphs (Octagonal Sleep Watch L; Ambulatory Monitoring, Inc.) for seven consecutive days. On two days (09:00-17:00h), behavioral observations of sleep (eyes closed with no purposeful movement) were conducted every 15 minutes by trained research staff, and the percent of observations asleep (observed %sleep) was calculated for each day. Actigraphy data for corresponding time periods were scored for sleep using three channels of activity measurement: zero-crossing mode (ZCM; Cole-Kripke PCD ZCM algorithm), time above threshold (TAT; UCSD TAT algorithm) and proportional integrating mode (PIM; UCSD PIM algorithm). The %sleep was calculated using each channel (ZCM, TAT and PIM %sleep; Action4 software; Ambulatory Monitoring, Inc.). Differences (observed minus actigraphy %sleep) and correlations between observed and actigraphy %sleep were calculated. The relationship between these difference scores and participant characteristics (age, illness burden, cognitive functioning, depression, premorbid and admission functional status, number of routine medications and reason for admission) were examined.

Results: The mean observed %sleep during the day was 16% (sd 13%). Based on actigraphy, %sleep was 14% (SD 13%) for TAT, 8% (SD 9%) for PIM and 10% (SD 10%) for ZCM. The mean difference in observed vs. actigraphy %sleep was 2% (SD 11%, 95%CI: -5.4 - 2.1) for TAT, 8% (SD 11%; 95%CI: -2.6 - 4.5) for PIM and 6% (SD 11%; 95%CI: -4.0 - 3.3) for ZCM. Pearson correlations between observed and actigraphy %sleep were: r=0.62 (p<.0005) for TAT, r=0.57 (p<.0005) for PIM and r=0.56 (p<.0005) for ZCM. Older age was associated with a greater discrepancy between observed and PIM %sleep (r=0.18, p=.040). Participants admitted for rehabilitation following general (non-orthopedic) surgical procedures had a greater discrepancy between observed and PIM %sleep compared to medical (mean difference: 6.3, p=.047) but not orthopedic (mean difference: 6.2, p=.059) participants. No other significant relationship between participant characteristics and the discrepancy between observed and actigraphy %sleep based on PIM, TAT or ZCM were found.

Conclusion: In the current study, the PIM channel was influenced by participant factors including age and specific medical problems. Selecting the most appropriate actigraphy channel for daytime sleep assessment may require consideration of such participant factors, and further research is needed in this area. Based on this comparison of observations versus actigraphy, the TAT channel showed the highest agreement with observations of daytime sleep, although the mean difference between the two was nontrivial. Despite the difficulty of PSG in the NH setting, comparison of these different activity channels to EEG is needed.

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Comparison of Respiratory Event Detection by a Polyvinylidene Fluoride film Airflow Sensor and a Pneumotachograph in Sleep Apnea Patients

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Introduction: Traditional thermal sensitive devices (thermocouples, thermistors) that have been used to detect airflow during sleep studies are limited by a slow response time and signal changes that are not proportional to changes in flow. Airflow sensors utilizing Polyvinylidene fluoride film (PVDF) have a more rapid response to changes in airflow and appear to more accurately detect changes in airflow than thermocouples or thermistors. The purpose of this study was to compare the ability of a PVDF sensor (Dymedix) and a pneumotachograph placed in a mask over the nose and mouth to detect respiratory events in patients with obstructive sleep apnea.

Methods: Ten male patients with known obstructive sleep apnea underwent polysomnography wearing a PVDF sensor (D) placed on the upper lip (sensing nasal and oral flow) and a tight fitting mask over the nose and mouth with a pneumotachograph (P) in the opening. A fluid filled esophageal catheter (E) was placed and chest and abdominal movements were also detected. Events were scored on 3 separate passes: D flow pass(no P or E tracings visible), P flow pass (no D or E tracings visible), E - pass (no D or P tracings visible). Apnea was defined on D or P flow tracings as fluctuations < 10% of baseline for 10 seconds or more in duration, Hypopnea1 as a 50% reduction in flow for 10 seconds or more in duration, Hypopnea2 any reduction in airflow for 10 seconds or more associated with a 3% drop in the SaO2 or followed by an arousal. Esophageal respiratory effort arousals (EREA)were defined as an arousal following a crescendo increase in the esophageal pressure deflections over at least 3 breaths or high (> 15 cm H2O) deflections followed by an arousal and an abrupt decrease in deflection. Respiratory arousals for the D and P sensors were defined as arousals associated with D Apnea + Hypopnea 2 and P Aapnea + Hypopnea 2 events respectively. The A +

Hypopnea 1 index and A + Hypopnea 2 index were compared for D and P flow sensors. Respiratory arousals-D, Respiratory arousals-P, and EERA were also compared.
Results: The A+Hypopnea 1 index (mean±SD) for the D sensor (20.1±27.1/hr) was less than the Pneumotach sensor (26.0 ±27.9/hr) (P <0.05). The (mean ±2 SD) difference for each subject was 6.1 ± 14.8 /hr. The correlation between the indices was 0.96 (P < 0.05). The A + Hypopnea 2 index for the D sensor (26.4±25.9) and Pneumotach (29.4±26.8/hr) were not different (P=NS). The mean ± 2 SD)difference for each subject was 3.0 ±8.5 /hr.For A + Hypopnea 2 index. The correlation between the D and P indices was .98 (P < 0.05) Respiratory arousals: The respiratory arousals for the D sensor (13.4 ±19.6), the pneumotach (13.9±20.1/hr), and the Esophageal catheter (12.4±21.3 /hr) were did not differ.
Conclusion: The PVDF (D) sensor gave slightly smaller AHIs compared to a "gold standard" accurate measure of airflow (the pneumotachograph - facemask system). The pneumotachograph signal showed flattening during obstructive hypopneas while the D sensor showed only a reduction in flow. Using the A + hypopnea 2 definition the mean difference in sensors was only 3/hr. On the basis of this study, the D sensor should satisfactorly detect respiratory events and respiratory arousals in most patients with obstructive sleep apnea. The accuracy of the signal compared favorably to the gold standard for detection of airflow (pneumotach - face mask). The PVDF sensor will likely be better tolerated by patients than a face mask and is easy to apply and use.

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A Novel Adaptive Wrist Actigraphy Algorithm For Sleep-Wake Detection In Sleep Apnea Patients

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Introduction: Actigraphy becomes increasingly important in detecting sleep/wakefulness during ambulatory sleep studies. However, current algorithms were developed primarily for normals and insomniacs, and are less accurate when studying sleep apnea patients. The parameters tested in most studies were sleep latency, sleep efficiency and total sleep time. In the current study, we assessed a novel automatic algorithm (the zzzPAT), which has been developed for actigraphic studies of normals and patients with obstructive sleep apnea syndrome (OSAS), by comparing it on an epoch-by-epoch basis to standard polysomnography (PSG).
Methods: Two hundreds and twenty eight subjects (38 normals and 190 patients with suspected OSAS) from 3 different sleep centers (Skara, Boston, Haifa) participated. All underwent a simultaneous study with both standard polysomnography and the Watch_PAT 100 (WP100), an ambulatory device with a built-in actigraph. The automatic sleep/wake algorithm, using a high-resolution raw actigraphy signal (100Hz sampling rate) and signal-processing techniques, is based on two main body movement characteristics. These include a quantification of both; (a) motion as measured by an energy detector, which corresponds to the magnitude and duration of the single, as well as, multiple successive movements; and (b) various periodic movement patterns, such as expected in moderate and severe OSAS patients.
Results: A total of 202260 epochs were compared between the novel actigraphic algorithm and a standard PSG (32112 epochs of normals, 48226, 73085, and 48837 of mild moderate and severe apnea patients, respectively. The overall sensitivity and specificity to detect sleep state (wake versus sleep) were 90% and 67%, respectively. The agreement ranged from 87% in the normals, through 86%, 85% and 80% in the mild, moderate and severe OSAS patients, respectively. There was a tight agreement between actigraphy and PSG in determining sleep efficiency (78.8 ± 13.4 vs 78.4 ± 9.9 %), total sleep time (690 ± 154 vs 690 ± 152 epochs) and sleep latency (43.3 ± 45.4 vs 56.8 ± 31.4 epochs) respectively.
Conclusion: We conclude that the zzzPAT algorithm using an actigraphic signal can accurately define sleep versus wakefulness in normal subjects and in patients with sleep apnea, on an epoch-by-epoch basis, and may therefore serve as an important tool to increase accuracy of OSA quantification in the home environment.

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Agreement Between Manual Scorers and an Automated Scoring System: Sleep Stages, Arousals, Respiratory Events, and Periodic Leg Movements of Sleep

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Introduction: The classification of sleep stages and quantification of arousals, sleep disordered breathing (SDB) events, and periodic leg movements are vital components of any polysomnogram (PSG). Manual scoring by a trained technologist remains the standard method for generating these data. However, this process is time-intensive and vulnerable to inter-scorer variability. Automated scoring (real-time or post-acquisition) offers the potential advantage of reduced cost, efficiency, and objectivity. Thus, we assessed one such automated scoring system, the Morpheus I Sleep Scoring System.
Methods: 31 digital PSG recordings were included in this study (all-night diagnostic PSGs for suspected SDB). All recordings used a standard montage for SDB including 4 EEG channels (C4-A1, C3-A2, O2-A1, O1-A2). Sleep stages were scored automatically using the automated scoring system (A) and manually by 2 registered PSG technologists (M1 and M2) according to Rechtschaffen and Kales. Arousals and periodic leg movements were also scored according to ASDA criteria. Respiratory events were scored according to recent AASM Medicare criteria. Each scorer was blinded to the results of the other scorers. Agreement and Cohen's Kappa were tabulated using: (a) a sleep stage epoch-by-epoch agreement matrix (5x5: W, S1, S2, SWS, REM), (b) an arousal scoring epoch-by-epoch agreement matrix (3x3: 0,1,2 arousals/epoch), (c) a respiratory event epoch-by-epoch agreement matrix (3x3: 0,1,2 events/epoch), and (d) a periodic leg movement epoch-by-epoch agreement matrix (3x3: 0,1,2 leg movements/epoch) for each pair. The automated algorithms used in this study are based on adaptive segmentation, fuzzy clustering, and hidden Markov models. The results are presented as mean ± standard deviation.
Results: All 31 recordings had sufficient signal fidelity for automated analysis. Measurements for scorers A, M1, and M2 included (mean±standard deviation): total sleep time (min) 357±65, 348±63, 345±61, sleep latency (min) 22±21, 26±24, 26±24, arousal index (arousals per hour of sleep) 22±16, 30±19, 36±17, apnea-hypopnea index (events per hour of sleep) 24±23, 21±23, 23±25, and periodic leg movement index (movements per hour of sleep) 19±25, 13±19, 16±21, respectively. The agreement and Cohen's Kappa were 78% & 0.67, 73% & 0.65, and 82% & 0.73 between pairs A-M1, A-M2, and M1-M2 for the 5x5 sleep stage agreement matrix. The arousal index agreement and Cohen's Kappa were 76% & 0.28, 76% & 0.30, and 84% & 0.57, apnea-hypopnea index agreement and Cohen's Kappa were 90% & 0.66, 90%

& 0.66, and 95% & 0.82, and periodic limb movement index agreement and Cohen's Kappa were 93% & 0.68, 92% & 0.66, and 96% & 0.77, respectively, between scoring pairs A-M1, A-M2, and M1-M2.
Conclusion: In a study population with prevalent SDB, agreement between manual scorers was close to the average pairwise agreement of 87% reported in the Sleep Heart Health Study (SHS). The automated classification of sleep stages was relatively close to this standard (A-M1 pair) and improved when stages 1 and 2 sleep were combined. There was also good agreement between automated and manual scoring of respiratory events and periodic leg movements. Manual editing of automated scoring may further improve this agreement and offer a significant advantage over manual scoring alone. Cohen's Kappa for the arousal scoring pairs suggests that inter-scorer agreement is poor regardless of the pair combination.

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New Measures for Sleep Quality and Sleep Depth
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WideMed Ltd., Omer, Israel

Introduction: Now days sleep quality and depth assessment is based on measures like sleep efficiency, sleep stages distribution and arousal index. None of these measures is good at predicting waking performance, thus not providing useful information. New visual evaluation of sleep quality and depth is presented. Evaluation is based on dynamic state modeling of brain's frequency activities during sleep. This study assessed the ability of offered evaluation in better distinguishing different patient groups. We believe that this ability will better predict waking performance.
Methods: Nine patients representing three groups were analyzed by Morpheus automatic scoring system. Group 1 included 3 patients with no significant sleep disorders (mean sleep efficiency 94%, mean SWS percentage 22.4%, mean arousal index 6.4 [1/h]). Group 2 included 3 patients with disordered sleep (mean sleep efficiency 52.7%, mean SWS percentage 5.3%, mean arousal index 13.2 [1/h]). Group 3 included 3 patients which apparently did not have significant sleep disorders (mean sleep efficiency 91.6%, mean SWS percentage 12.7% and mean arousal index 5.7 [1/h]). A dynamic four brain frequency states model including "high frequency" (HF), "low energy mixed frequency" (HF1), "high energy mixed frequency" (HF2) and "low frequency" (LF) states was applied for each patient. EEG signals were adaptively segmented into quasi stationary segments, enabling micro sleep and sleep fragmentation analysis. Patient intrinsic states were adaptively recognized using fuzzy clustering of features extracted form EEG segments. Membership levels in each state were then attributed to each EEG segment, creating membership functions, which sketch a continuous measurement of intrinsic brain activity. The following charts were plotted as a function of time: 1) EEG fundamental frequency, 2) averaged membership in LF (sleep depth level), 3) averaged membership in each state, 4) accumulated duration of each state, 5) wake level versus sleep level.
Results: Charts of each group revealed the following results: Group 1: 1) clear trends of fundamental frequency below 4 Hz, 2) observable sleep depth level above 80%, 3) minor temporal overlapping between HF and MF-2 or LF averaged membership functions, 4) low accumulation rate of HF duration during sleep, 5) most time sleep level was above 80%. Group 2: 1) rarely observed fundamental frequency below 4 Hz, 2) sleep depth level reaches above 50% rarely, 3) observed temporal overlapping between HF and MF2 averaged membership functions, most time membership in HF was highest, 4) high accumulation rate of HF duration, 5) most time sleep level was below 20%. Group 3: 1) clear trends of fundamental frequency below 4 Hz, 2) observable sleep depth level above 50%, 3) Observable temporal overlapping between HF and MF2 or LF averaged membership functions, 4) high accumulation rate of HF duration during sleep indicating of sleep fragmentation, 5) Sleep level reaches much lower values compared to group1.
Conclusion: The charts showed significant differences between all group pairs, especially between group1 and group3 which was not significantly distinguishable by standard measures. Therefore we believe that numerical measures based on offered evaluation, can be used for accurate continuous quantification of sleep quality and depth which can be utilized for CPAP automatic titration, anesthesia control and for assistance in CHF prediction.

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Validation of a Commercially Available Rodent Polysomnographic Scoring System
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Introduction: We have assessed the sensitivity and specificity of a commercially available rodent scoring plug-in module (Rodent scoring module V1.0, Medcare, Iceland) that integrates seamlessly into the Somnologica Science polysomnography platform (Medcare, Iceland). This plug-in module performs feature extractions in four signals simultaneously: a) cortical EEG, b) hippocampal theta EEG, c) EMG and d)locomotor activity if available. The feature extraction is based on frequency estimation for EEG channels and amplitude discrimination for the EMG and activity. These features are then used to determine probabilities that the EEG and EMG frequency/amplitude components within each discrete epoch best represent waking, sleeping or rapid eye movement (REM). A consensus of the probabilities is used to determine the final results.
Methods: Polysomnographic data was collected from five adult rats, each over a 24-hour period. A single observer then scored each record in 15-second epochs as either wake (W), delta sleep(DS), or REM sleep. Wake was defined by the presence of low amplitude fast frequency EEG in conjunction with moderate to high amplitude EMG. Delta sleep was defined by the presence of high amplitude low frequency delta wave activity that occupied at least 30% of the epoch, in conjunction with a low amplitude EMG. REM sleep was defined by the presence of hypersynchronous theta wave activity centered near 7.0 Hz, low amplitude fast frequency EEG and EMG activity at its nadir (allowing for phasic activity). Once each polysomnographic record had been manually scored, the rodent scoring plug-in module was used to score each file. Kappa coefficients were used to determine levels of agreement between these two scoring methods for each rat's 24-hour data file.
Results: Levels of agreement between the five hand-scored and automated scored files for each rat were: a) 80.7% (kappa 0.60), b) 88.5% (kappa 0.79), c) 91.1% (kappa 0.82), d) 92.4% (kappa 0.87) and e) 93.0% (kappa 0.87), yielding a mean agreement level of 89% (kappa 0.80). We determined the automated scoring program's specificity for determining W to be 87.4%, DS to be 95.1%, and REM to be 83.6%.
Conclusion: Significant levels of agreement were achieved between polysomnographic variables scored manually and then automatically with the rodent scoring plug-in module. We conclude that this automated scoring algorithm, which seamlessly interfaces with a commercially available software platform, can reliably score rodent polysomnographic data. However, manual review and editing of files is necessary to ensure that absolute accuracy is achieved. Additional validations of newly developed features such as user defined epochs of wake, sleep and REM which are used by the algorithm to increase its recognition of these

states suggest higher levels of agreement between manual and automated scoring are feasible.

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Comparison of Total Sleep Time from Actigraphy and Polysomnography in Older Women: The SOF Study

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Introduction: Polysomnography (PSG) is considered the gold standard in assessing sleep but it can be costly and difficult to gather in a large epidemiologic study. Actigraphy is less invasive and less expensive than PSG. Our study examines the comparability of 3 modes of actigraphy to unattended in-home PSG in 66 elderly community dwelling women.
Methods: The Study of Osteoporotic Fractures (SOF) enrolled 9704 Caucasian women from 1986 to 1988. In 1996 662 African American women were added. In 2002, 4584 women returned for their eighth visit. Actigraphy data was collected using the SleepWatch-O® (Ambulatory Monitoring, Inc). Data were gathered in 3 modes: zero crossings (ZCM), digital integration (DIM) and time above threshold (TAT). Action-W version 2 software was used to analyze the actigraphy data. Unattended overnight 12 channel in-home PSG data was collected on a subset of 436 women using the Compumedics Siesta Unit. For the PSG studies, sleep was staged from the EEG, EMG, and EOG channels using standard criteria by certified scorers blinded to the results of the actigraphy studies. All staff acquiring the PSG and/or actigraphy data were trained and certified. The actigraphy data was truncated to match the recording times from the PSG collection. 66 women had actigraphy and PSG data collected concurrently. Their average age was 82.0(SD=3.7) and 5.5% were African American. Differences in characteristics of the analysis subgroup and the remaining SOF population were examined using t-tests or Wilcoxon rank sum tests for continuous data and chi-squared tests for categorical data. Differences in total sleep time (TST) between PSG and actigraphy data were examined with correlations and paired t-tests.
Results: Our subset of 66 women was comparable to the remaining SOF study in race, physical function, smoking, sleep medication use, self reported health, depression, cognition, and total sleep time (TST) from actigraphy and PSG (all $p>0.09$). Significant, but small to modest, differences were observed for age and body mass index (BMI) compared to the remaining SOF cohort (younger by 1.65 years, higher BMI by 2.00 kg/m2 $p<0.05$). The average collection time was 7.6 hours (SD=1.3). The average TST from PSG was 5.7 hours (SD=1.2). The average hours of TST from the three modes of actigraphy were ZCM: 5.3 hours (SD=1.9); DIM: 6.1 hours (SD=1.4); and TAT: 6.4 hours (SD=1.5). While the PSG to actigraphy paired t-tests on TST were $p<0.05$ for all 3 modes, the correlations of TST gathered from PSG to the actigraphy modes of ZCM (0.60), DIM (0.78), and TAT (0.76) were moderate to high. On average, the DIM actigraphy mode only overestimated TST by 18.3 minutes when compared to PSG (ZCM overestimated by 40.8 minutes, TAT underestimated by 24.4 minutes). The TST from actigraphy data for many participants was within 30 minutes of PSG: ZCM 48.5% within 30 minutes, DIM 32.5% and TAT 15.3%. TST computed from DIM was >=2 hours from the PSG TST only 2.2% of the time, ZCM 15.2%, and TAT 4.4%.
Conclusion: There is a significant difference between TST from actigraphy and PSG. However, actigraphy is highly predictive of PSG and can be a good surrogate measure in large epidemiologic studies for convenience and cost. Of the 3 modes of actigraphy examined, the digital integration mode correlated higher with PSG and had fewer participants with large differences in our population of community dwelling women age 73 to 92.

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Alertness Level Plateau Following Application Of nCPAP

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Introduction: Nasal Continuous Positive Airway Pressure (nCPAP) has been the recommended treatment for Sleep Disordered Breathing (SDB) since 1981. One of the sequelae of untreated SDB is a deficit in neurocognitive function including alertness levels. This study looks at changes in Psychomotor Vigilance Task (PVT) reaction time from before treatment to after treatment. Patient utilization of nCPAP was tracked on a daily basis by a new type of compliance monitoring system developed by Sunrise Medical. This study was approved by our IRB, and all patients signed Informed Consent.
Methods: Nine prospective patients undergoing evaluation for SDB were invited to participate in the study. All subjects completed three baseline PVT sessions prior to undergoing PSG testing. Following the three PVT sessions, all subjects underwent either a Split-Night Polysomnogram or Diagnostic Polysomnogram followed by nCPAP Titration. After receiving their nCPAP machines (DeVilbiss 9001 units with heated humidifiers) with the ecompliance download module the subjects returned to the KSDSDC for 10 to 14 daily PVT sessions, excepting weekends and holidays. Six daytime staff members of the KSDSDC served as a control group, with each staff member recording 10 consecutive daily PVT sessions, again weekends and holidays excepted. All PVT sessions had identical recording parameters: Trial length of 10 minutes, minimum interval of 1000 ms, and maximum interval of 7000 ms. and were recorded at approximately the same time each day.
Results: Eight of the nine participants had an overall decrease in mean Reaction Time. The ninth subject still had significant apnea at the best CPAP level found, and her mean RT increased over time. Of the eight subjects that improved, the mean decrease in RT was 10.3% (1.83% to 32.04%). The control group did not show a statistically significant change over time in mean RT. However, the subject group did show a statistically significant change in RT, from a mean of 290.08 ms to a mean of 265.31 ms ($p=0.029$). The subject group had statistically significant slower mean Reaction Times before CPAP application than the control group; Controls = 268.85 ms, Subjects = 290.08 ms ($p=0.050$). Following 2 weeks of CPAP use there was no statistically significant difference in mean RT between the control and subject groups; Controls = 264.31 ms, Subjects = 265.31 ms ($p=0.9360$) The improvement in mean RT for the subject group began after the first night on CPAP. Of patients that showed improvement, 63% of the improvement occurred after the first night of CPAP usage.
Conclusion: This small study indicates that patients with untreated SDB have slower reaction times as measured by PVT than normal controls. It also shows that in some patients with SDB, who are treated with CPAP, the reaction time quickly improves to the range of normal controls. The

improvement in reaction time generally begins after the first night with CPAP. There did not appear to be a significant learning effect for the PVT. The ecompliance module developed by DeVilbiss proved to be an excellent method of tracking day-to-day compliance in patients.

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Actigraphy Detects Microvibration Life Signs Patterns in a Patient Transitioning from Coma to Death

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Introduction: An ongoing study investigates the relationship of peripheral microvibrations (microtremor) to the clinical course of coma patients for the purpose of determining whether actigraphy can distinguish coma from sleep, and for future field usage in discriminating traumatic unconsciousness from death. The present report describes the microvibration patterns observed in a single Glasgow Coma Level Three patient who expired while the wrist device was applied. A new version of the actigraph device permits high resolution recording of fine movements (microvibrations and tremors) which may be analyzed by more complex mathematical techniques. Both periodic transients (coupled to breathing and heartbeat) and stochastic components (physiological tremor) may be described in these signals. Whether such signal characteristics can be usefully related to corresponding changes in sleep levels or clinical status is under study, but in any event, their occurrence is consistent with life. Their dissipation during the transition from life to death is rarely observed, and this report is presented to highlight the potential use of actigraphy in life signs monitoring.
Methods: The Ballistic Actigraph (Precision Control Design, Inc, Fort Walton Beach, Fl) was applied to the wrist of a stroke patient in Glasgow Coma Level 3. The 1.2 oz actigraph consists of linear piezoelectric accelerometer mounted in a watch case. Movements on the anterior-posterior axis of the wrist are digitally sampled 32 times a second and recorded with 12-bit resolution. The 3-db passband is 0.1 to 14 Hz, and sensitivity is +/- 0.5 mV for .002g acceleration. 48 hrs of signal were recorded, and 7 hrs of data were used to calculate amplitude, variance, and spectral content for each 30-second interval. Consent was obtained from next-of-kin. The protocol was WRAIR IRB approved and complied with all Federal standards for human research.
Results: Analysis revealed a complex mixture of signals compatible with heart beat, breathing, and microtremor above a 2.5 mV (root-mean-square (RMS)) noise floor. Amplitude following the cessation of assisted ventilation rose from about 60 mV RMS to 200 mV. During the last 3.5 hours of life, RMS amplitude, signal variance and complexity of both the time series and the power spectrum decreased almost linearly to the noise floor. Median spectral frequency increased from about 2.5 Hz to nearly 5 Hz during the last two hours. Regular rhythmic spindle shaped transients occurred at a rate of 15-25 /min in a pattern consistent with respiration, and at about 80-90 /min consistent with ballistocardiographic impulse. As transition to death approached, irregularity and slowing of respiratory waves occurred in a pattern that might be considered agonal.
Conclusion: Actigraphy detects intrinsic microvibrations in a deeply comatose patient, and discerns rhythmic patterns consistent with heartbeat, breathing, and physiological tremor. Impending death is signaled by a decay and cessation of these signal characteristics. This case provides support for the potential usefulness of actigraphy as a method of distinguishing sleep from coma, and for monitoring life signs in an immobile and unconscious patient.

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Comparison of Sleep Assessment Devices in a Mixed Sample of Sleep Disordered Patients: An Update

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Introduction: Polysomnography (PSG) is the gold standard measure of objective sleep, but it is a costly and burdensome procedure. Alternative methodologies such as actigraphy (ACT), sleep logs (SL), and REMView™ (RV; Respironics, Inc., Pittsburgh, PA) provide estimates of sleep-wake parameters, yet data directly comparing these various sleep assessment devices with PSG are lacking. This report updates our 2003 APSS abstract by using a larger sample of sleep-disordered patients to compare the performance of RV, ACT, and SL against PSG for estimating common sleep parameters.
Methods: Participants were 57 (53 male) VA primary care outpatients (M age = 58.0 yrs., SD = 13.1 yrs.) undergoing screening procedures for an insomnia treatment study. Each participant underwent structured psychiatric (SCID) and sleep (SISD) diagnostic interviews. Eligible participants were scheduled for one night of ambulatory PSG with Compumedics© ambulatory recorders. Participants slept unattended on the hospital lodging unit. On this night of PSG recording, participants also wore an Actiwatch-L (Mini-Mitter Co., Inc., Bend, OR) actigraph on their non-dominant wrist and the RV device. They completed a sleep log the following morning. These devices yielded estimates of time in bed (TIB), total sleep time (TST), total wake time (TWT), sleep onset latency (SOL), sleep efficiency (SE), and wake after sleep onset (WASO) that were subsequently compared to corresponding PSG-derived values.
Results: Eighteen patients were diagnosed with inadequate sleep hygiene, 17 with sleep apnea, 11 with psychophysiological insomnia, 5 with insomnia associated with an anxiety or mood disorder, 3 with periodic limb movement disorder, 2 with a dual diagnosis of sleep apnea and insomnia, and 1 with hypnotic-dependent sleep disorder. Thirty patients had at least one current or past DSM-IV Axis I psychiatric diagnosis. Pearson correlations between sleep devices were calculated and compared to PSG. Repeated-measures ANOVA with Dunnetts adjustment for multiple comparisons was used to investigate mean differences between PSG and the other devices. Correlations between ACT and PSG ranged from .64 - .95. ACT significantly overestimated SE and TST and underestimated TWT and WASO. RV-PSG correlations ranged from .67 - .97; RV overestimated SOL and underestimated WASO. SL-PSG correlations ranged from .45 - .79; SL overestimated SOL and TWT while underestimating TIB, SE, and TST.
Conclusion: These data replicate our previous findings that alternative sleep assessment methodologies show moderate to high correlations with sleep measures from PSG, and the accuracy of different devices varies depending on the sleep parameter of interest. ACT reliably and accurately measured TIB and SOL, whereas RV yielded reliable and accurate measurements of TIB, SE, TWT, and TST. WASO was the only sleep parameter measured both accurately and reliably by SL, affirming the subjective nature of this measurement device.

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Comparison of Peak Flow to Tidal Volume Using a Pneumotrach in the Laboratory

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Introduction: Polysomnographic (PSG) monitoring traditionally utilizes a variety of sensors to generate an airflow waveform that is not a direct measure of either flow or inspired volume. The definitions of apnea and hypopnea incorporate the parameter of airflow. PSG analysis typically looks at reductions in the waveform peaks to identify potential obstructive events with the implicit assumption that the waveform peaks are a direct correlate of actual airflow. A true obstructive event will result in lower air exchange, or volume. We set out to test the hypothesis that peak flow is equivalent to tidal volume. Realizing that measures of tidal volume are encumbering and difficult, we used a pneumotach in a laboratory, rather than a clinical, setting.
Methods: 10 healthy adults (mean age 38, range 23-56) underwent airflow monitoring with the Hans Rudolph pneumotach system. Each subject was subjected to three trains of 20 breaths wherein rates or volumes were independently varied from minimal to maximal capacities as well as the full range between these levels. Peak expiratory flow and expiratory volume for each expiratory phase of the respiratory cycle were measured. Peak flow and volume measurements were compared and correlation statistics generated for all respiratory cycles collected.
Results: Of the 10 subjects, one was eliminated due to pneumotach mask incompatibility. Comparison of peak flow versus the tidal volume showed poor correlation over the full range of peak flow levels. Correlation coefficients : r = 0.57, r2 = 0.33, p-value = 0.0002.
Conclusion: Peak flow did not correlate well to tidal volume in this controlled setting. This raises serious questions as to whether current technology in general, and peak flow monitoring specifically, is adequate to actually measure obstructive events as currently defined. Further exploration of the relationship between peak flow and tidal volume in subjects suffering from sleep-related breathing disturbance syndrome during PSG is warranted to determine if the use of tidal volume would result in clinically superior identification of obstructive events.

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Pupillary Unrest in Sleepy versus Non-Sleepy Healthy Subjects

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Introduction: In behaviorally and subjectively sleepy individuals the size of the pupils has been observed to oscillate significantly more than in alert individuals. Little information is available about how the PUI, a mathematical way of quantifying this oscillation, compares as an objective measure of physiologic sleepiness to the Multiple Sleep Latency Test (MSLT). The purpose of this presentation is to compare the PUI and sleep latencies in healthy sleepy (9 M, 10 F, 20-53 years of age) versus healthy non-sleepy (11 M, 16 F, 22-61 years of age) subjects.
Methods: Health screening included: 1.) a review of prior medical records; 2.) completion of the Sleep Disorders Questionnaire, the Beck Depression Inventory and a Sleep Log; and 3.) a clinic visit including a urine drug screen (UDS), selected blood tests, a urinanalysis, an EKG and a complete medical history and physical examination. A PSG was administered the night prior to the MSLT (conducted at 1000, 1200, 1400 and 1600 hours), and pupillometry alertness level (ALT) daytime testing (conducted at 900, 1100, 1300 and 1500 hours) about two weeks after screening data were determined to be normal. During ALT testing with the Pupillographic Sleepiness Test(PST) AMTech GmbH pupillometer, subjects were comfortably seated in a quiet, dark room with instructions to keep their eyes open and try to stay awake. Between the MSLT and ALT sessions, another UDS and four subjective sleepiness measures were administered.
Results: Controls with a mean sleep latency (SL) of < 10 minutes were classified as sleepy (mean SL of sleepy and non-sleepy subjects were 6.1+/-2.9 versus 15+/-2.7 minutes, t44 = 10.7, p .01). Between groups analyses revealed the following non-significant statistical results: 1.) no differences in age and gender were found; 2.) no differences in mean scores on the Epworth Sleepiness Scale (sleepy subjects = 5.9+/-3.1 versus non-sleepy = 5.6+/-3) and the Functional Outcomes of Sleepiness Scale were found (sleepy and non-sleepy subjects were 18.5+/-2.1 and 18.7+/-1.7); 3.) mean minutes of sleep the night of PSG testing were 442.5+/-82 and 412.9+/-51.4 for sleepy and non-sleepy subjects respectively. Analyses of objective measures revealed the following: 1.) MANCOVA (with minutes of sleep on the previous night PSG as the covariate) for the mean PUI and SL between groups revealed significant differences across the four testing periods (F1, 43 = 5.8, p < .05 and F1, 43 = 106.6, p < .01 respectively); 2.) repeated measures ANCOVA for the mean SL (F3, 41 = 6.8, p < .01) between time periods across the groups revealed that subjects stayed awake significantly longer on Nap 4 compared to the other 3 time periods; 3.) repeated measures ANCOVA for the mean PUI showed a trend towards being significantly higher during the 1300 hours ALT session for sleepy subjects.
Conclusion: The PUI is capable of distinguishing between sleepy and non-sleepy healthy subjects, and could be useful in situations where the level of sleepiness is the outcome of interest. Further research is needed to establish PUI norms for healthy non-sleepy subjects by age and gender.

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Bilateral Comparisons of Online Signals of a Disposable Electronic Bruxism Device and Masseter EMG Bruxism Events

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Introduction: We have previously presented the BiteStrip bruxism device, a miniature, disposable electronic screener with EMG electrodes designed to identify masseter muscle contractions exceeding a predetermined individual threshold. BiteStrip scores were highly correlated with masseter EMG scored for bruxing events. In the present study, online BiteStrip signals were recorded and compared with bilateral masseter EMG tracings during overnight polysomnography (PSG). The goals of the study were to evaluate measures of accuracy of the BiteStrip signal against "gold standard" masseter EMG scored for bruxing events, and to assess bilateral differences in the number of bruxism events, as well as in patterns of bruxism activity throughout the night.
Methods: Nine subjects participated in an overnight PSG sleep lab

study. Three were referred due to snoring and suspected sleep apnea syndrome and six were referred from a temporomandibular disorders (TMD) clinic. All were suspected of sleep bruxism based on subjective reports. To record the BiteStrip signal online, the BiteStrip software was programmed to emit a red blink of light for each detected bruxism event. Output was transmitted via an optical interface and displayed as an all-or-none signal on a PSG channel. Bilateral recordings were performed both for masseter EMG and for BiteStrips, in addition to traditional PSG signals. An experienced scorer scored each EMG and each BiteStrip channel blinded to other channels. Bruxism events were scored as such if a phasic and / or tonic increase of EMG tonus exceeded 30% of the maximal voluntary clench (MVC) (determined before subject fell asleep) and lasted >0.25 second. Bilateral comparisons were made between left and right EMG bruxism events and left and right BiteStrip signals. For measures of accuracy of BiteStrip signals against EMG bruxism events, the number of true positives, false positives and false negatives were counted, and sensitivity and positive predictive value (PPV) computed.

Results: Data was obtained from nine subjects (6 males) aged 33.4 (range: 18-65). Means (and standard deviations) of the EMG and BiteStrip scores of sleep lab vs. TMD clinic patients were 38.7 (11.6) and 60.2 (22.7) (sleep lab) and 208.0 (161.1) and 176.0 (115.8) (TMD clinic) respectively. Nonparametric Mann Whitney tests were significant for both EMG and BiteStrip between-group differences ($p<0.01$). Means (and standard deviations) for left and right EMG scores: 156.9 (158.7) and 146.2 (157.8); BiteStrip scores: 144.2 (114.8) and 130.6 (110.3) respectively. Nonparametric paired tests (Wilcoxon) showed no significant bilateral differences for EMG or BiteStrip scores. Bruxism patterns (graphs not shown), based on visual inspection, were concomitant for left and right masseters. Spearman's rho correlations were significant for left and right EMG scores ($r=0.93$, $p<0.001$) and BiteStrip scores ($r=0.83$, $p<0.01$). Spearman's rho correlation between all EMG and BiteStrip scores was significant ($r=0.88$, $p<0.001$). Average sensitivity was 0.75. Average PPV was 0.73.

Conclusion: Bilateral differences in bruxism are small. EMG and BiteStrip scores show a strong positive relationship. Sensitivity and PPV of the BiteStrip are good.

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The Role of Actigraphy in the Study of Sleep and Circadian Rhythms

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Introduction: Several review papers have concluded that wrist actigraphy is reliable and valid for detecting sleep in normal, healthy adults. Although it is not indicated for the routine diagnosis, assessment of severity, or management of any of the sleep disorders it may be useful in characterising and monitoring of insomnia, circadian rhythm disorders, restless legs syndrome/periodic limb movement disorder and excessive sleepiness.

Methods: For this study 100 consecutive, non-dominant wrist, actigraphy studies (Cambridge Neurotechnology) are grouped into bands that describe their reason for referral. The final diagnosis of each study was noted and related to referral band.

Results: The group included 44 females and 56 males, with age ranging from 15 to 75 yrs. The six referral bands include insomnia 36% (I), excessive daytime sleepiness 34% (EDS), circadian disorder 15% (C), periodic leg movement disorder 4% (PLMD), sleep hygiene issues 5% (H) and others 6% (O). The outcomes were divided into seven categories: fragmented sleep (fr), inadequate sleep opportunity (iso), hypersomnolence (h), circadian disorder (c), poor hygiene (hy), insomnia (i) and sleep state misperception (ssm). Of the insomnia band 41% were confirmed as having insomnia or other related sleep disorder (fr, c and i) and the remaining 59% were diagnosed as iso, hy and ssm. Sixty five percent of the referral band EDS were accounted for by fr, h and c with the residual 35% in iso and hy. Ninety three percent of the referral band C were confirmed as either c, i, or fr with the resulting 7% diagnosed as hy.

Conclusion: Clinical actigraphy with simultaneous completion of a sleep log is very useful in characterising I and C and assessing EDS. The ability to distinguish in band I those patients with iso, hy and ssm enables appropriate treatment of these groups. Similarly confirmation of circadian disorders in C guides pharmaco or phototherapy, while reduced sleep opportunity (iso and hy) is clearly important to identify in EDS. This relatively in-expensive home based tool can help provide efficient and effective management of a broad range of sleep disorders.

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SleepXML - Extensible Markup Language (XML) Application For Polysomnographic (PSG) Data Storage And Exchange

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Introduction: Although several standards (eg EDF - European Data Format) exist for PSG data interchange that deal adequately with raw data, processed data (e.g. sleep stage scores, respiratory scores, tabulations and reports), which are necessary for a complete description of a polysomnogram, are handled less well. XML (eXtensible Markup Language) is a standard defined by the World Wide Web Consortium (W3C) that provides a flexible, extensible, non-proprietary, open electronic format capable of describing both data and meta-data in the same document and is well suited to use in polysomnography. Much the same way browsers allow cross platform display and processing of a web page, this approach allows interchange and display of data while preserving existing inter-lab and inter-PSG system differences in defined event sets. This abstract proposes an XML dialect for PSG purposes (SleepXML). We demonstrate its feasibility by creating a simple program to utilize a SleepXML file and reproduce many of the functions needed for PSG analysis. We demonstrate its flexibility by converting a file of SleepXML PSG events (as might be generated from collection and scoring done in a proprietary system which exported its data in this format) to a different set of events (as might be used by a different PSG system).

Methods: In the SleepXML dialect, raw data is left unchanged and PSG events are fully defined by the XML Schema. SleepXML schema defines PSG channel types (such as Airflow, Snore, SaO2) and PSG events on those channels. Event parameters (start time, duration, type, etc.) are defined via XML child elements or XML attributes. Event characteristics, such as SaO2 drop for a hypopnea, can be defined for specific events. Characteristics of event display, such as screen color, and scoring preferences (e.g. shortcut keystrokes) are also defined via the SleepXML attributes. For report purposes graphics (e.g. PSG hypnogram and SaO2/Pulse trend) are saved to XML-based Scalable Vector Graphics (SVG) format and presented in a browser-compatible HTML report. Calculated statistics such as sleep stage specific AHI are stored as a hierarchical XML document. Data presentation on the computer screen is defined via another W3C standard - XSLT, which is used to transform XML data to HTML display tags. Because XML is compatible with existing database systems, all SleepXML data can be readily imported into existing databases (e.g. an SQL database containing patient information and questionnaire data). In order to test transformation of one PSG system's event types to those used in another system, an XSLT transformation was written.

Results: To evaluate feasibility, software was written that can display, score and tabulate a set of PSG events based entirely on the information contained within the SleepXML data definitions contained in the PSG. To evaluate flexibility, several different event set definitions from different sleep labs were presented in XML Schema format and XSLT transformations were created for conversion of score files from one event set definition to another. Sleep records were scored based on different event definitions and later the score files were successfully converted from one format to another, allowing for different lab scores to be reviewed with a single SleepXML-aware software package.
Conclusion: The obtained results show that SleepXML has the potential to provide a useful platform for describing, storing, and transforming/exchanging polysomnographic data and events.

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An Analysis of Variance Between Three Methods of Monitoring Oral/Nasal Airflow for the Detection of Apneas, Hypopneas and Hypoventilation During Nocturnal Polysomnogram

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Introduction: Thermocouple, which is a measurement of respiratory gas temperature and differential pressure transducer are both used to identify degrees of airway obstruction during diagnostic polysomnograms. Capnography (EtCO2), the measurement of respiratory gas concentration of CO2, generates a waveform as a function of respiratory gas concentration as well as a quantitative value reflective of arterial CO2. The objective of the current study was to assess the sensitivity and specificity of capnography as compared with oral/nasal thermocouple and pressure transducer in the detection of apneas, hypopneas and hypoventilation in the sleep laboratory environment.
Methods: 82 subjects, 49 males and 33 females, mean age 44.7 years, and mean BMI 33.8 kg/m2, were studied in an American Academy of Sleep Medicine (AASM) accredited Sleep Disorder Center and scored per AASM Guidelines. Data collection included the following channels: EEG, EOG, submental chin and leg EMG, ECG, Oral/Nasal Airflow (thermocouple, pressure transducer and EtCO2), Thoracic Effort, Abdominal Effort and Pulse Oximetry. Eight Polysomnographic Technologists performed blind respiratory event analysis, with inter-scorer reliability of 95%. Each scoring team was assigned to score using one of three flow channels.
Results: Data was analyzed using repeated measures analysis of variance (ANOVA). No significant differences were found between EtCO2, thermocouple and pressure for identification of apnea, hypopnea or respiratory disturbance index. Analysis supported the hypothesis: no significant differences were found between capnography, thermocouple and/or pressure transducer monitoring techniques. Capnography did detect hypoventilation (EtCO2 > 50 mmHg > 10% of total sleep time) in 3 subjects.
Conclusion: This study demonstrates that capnography is able to identify apneas and hypopneas in a sleep laboratory environment with the same sensitivity and specificity as thermocouple and pressure monitoring techniques. Additionally, quantitative EtCO2 monitoring has the potential to identify clinically significant hypoventilation not apparent using qualitative airflow monitoring techniques. Capnography may be more useful than thermocouple or pressure for noninvasive monitoring during sleep.

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Analysis Of MSLT Using 10 Compared With 30-Second Epochs Changes The Test Conclusion In 3/10 Patients Referred With EDS

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Introduction: The multiple sleep latency test (MSLT) is useful in the assessment and diagnosis of disorders of excessive sleepiness. Sleep stages during the MSLT are analysed by the standard Rechtschaffen and Kales criteria using 30-sec epoch lengths, mainly for convenience. The results of the MSLT can be placed in one of three categories: 1. Sleep onset <5mins indicates pathological sleepiness, 2. Sleep onset between 5 - 10 mins is equivocal, 3. Sleep onset >10mins is normal (Carskadon et al 1986). An equivocal result is the most difficult to interpret, clinically. We looked at equivocal MSLTs to determine whether using a shorter epoch would affect the test conclusions.
Methods: We studied 10 consecutive equivocal MSLT results from patients referred with excessive daytime sleepiness. All patients had overnight polysomnography followed by an MSLT. Four trials were conducted at two-hour intervals starting at 9:00am, about two hours after waking. The same scorer scored each trial manually using standard 30-sec epochs. The results were then reanalyed using 10-sec epochs.
Results: The use of 10-sec epochs changed the test conclusions in 3/10 patients: 2 patients' results went from equivocal to pathological sleepiness and 1 patient's result became normal. However, there was no statistical difference ($p = 0.23$) when the sleep onset scores from the 10-sec and 30-sec epoch groups were compared using a paired Students t-test.
Conclusion: Our results suggest that the use of a short, 10-sec, epoch in the analysis of MSLTs allows more clear-cut conclusions with substantially fewer equivocal results. However, this analysis is more time consuming than the standard 30-sec method and it does not make a statistical difference to sleep onset scores.

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The Maintenance of Wakefulness Test is the Principal Measure of Excessive Daytime Sleepiness in Narcolepsy/Cataplexy Using Principal Component Analysis

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Introduction: There is debate about the best test for detecting excessive daytime sleepiness. Objective measures include the Maintenance of Wakefulness Test (MWT) and Multiple Sleep Latency Test (MSLT). Subjective measures include the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), and the Visual Analogue Sleepiness Scale (VASS). The aim of this study was to determine which of these tests is the principal measure of excessive daytime sleepiness (EDS) in patients with narcolepsy/cataplexy using the statistical technique of principal component analysis (PCA).
Methods: We studied the sleep test results of 20 patients with narcolepsy/cataplexy attending the Walton Centre Sleep Clinic. Each patient had previously completed an ESS followed by nocturnal polysomnography and a standard four trial MWT and MSLT test protocol, on the same day, 2 hours after waking. The SSS and VASS were obtained after each MWT trial. The same technician scored each MWT and MSLT trial manually. Mean scores were calculated for the MWT, MSLT, SSS, and VASS. All scores were entered into a database (SPSS 11.0) and analysed using a

PCA extraction method.
Results: Using PCA and Kaiser criteria (eigen values greater than 1) a single component was extracted. This result was confirmed using the graphical scree test. Final communality estimates, which are the proportion of variance of the variables accounted for by the common factors, were calculated. The MWT variable had the largest extracted communality score of 0.84.
Conclusion: Our analysis suggests that the MWT is the principal component of the standard battery of sleep tests for detecting excessive daytime sleepiness in narcolepsy/cataplexy patients. However, in the diagnosis of patients with narcolepsy/cataplexy, the MWT should only be used to supplement information from other tests as it does not help characterize the sleepiness.

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Differentiation of Sleep Stages and Sleep Apnea by Detrended Fluctuation Analysis of Heart Rate Variability is Better than Spectral Analysis

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Introduction: The autonomous nervous system changes its activities with sleep. Sympathetic tone drops from wakefulness over sleep stages 1 to 4. During REM sleep high but irregular activities are observed. Heart rate is an easy accessible surrogate for sympathetic activity. Heart rate is also influenced by disorders such as sleep apnea. Along with sleep apnea cyclical variations of heart rate are so characteristic that they were used to detect sleep apnea. In a systematic study we compared the performance of spectral analysis and detrended fluctuation analysis (DFA) to discriminate sleep stages and sleep apnea at the same time.
Methods: Fourteen healthy subjects, 33 patients with moderate (AHI < 40/hour), and 31 patients with severe sleep apnea (AHI > 40/hour) were investigated using cardiorespiratory polysomnography. Beat-to-beat intervals were calculated based on a single lead ECG. Artifacts and ectopic beats were removed. Only those recordings were considered where less than 1% of data were disturbed. DFA was applied to epochs of continuous sleep stages (wake, light sleep, slow wave sleep, REM sleep) separately and then averaged. Based on DFA two scaling parameters were derived. To characterize short time scales an exponent was calculated for 10 to 40 heart beats and to characterize longer time scales an exponent for 70 to 300 beats was calculated. Spectral analysis was applied to the same heart rate segments. From spectral analysis power established frequency bands were derived. The VLF component (< 0.04 Hz), the LF component (0.04 - 0.15 Hz), the HF component (0.15 - 0.4 Hz) as well as the sympathovagal balance (LF/HF) were computed. Mean heart rate value and standard deviation was also calculated. Discriminance analysis was used on a person and sleep stage basis to compare the two methods for a successful separation of sleep stages and sleep apnea severity.
Results: The spectral parameters VLF, LF, HF, and LF/HF confirmed decreasing sympathetic and increasing parasympathetic activity from wakefulness and REM over light sleep to deep sleep. The parasympathetic increase is reduced in patients with sleep apnea. Using discriminance analysis decision a linear model was created to distinguish sleep stages and sleep apnea severity. Using the spectral parameters 69.7% of the apnea severity assignments and 54.6% of the sleep stage assignments were correct. Using scaling analysis assignments increased to 74.4% and 85.0%, respectively. Changes in heart rate variability are better quantified by scaling analysis than by spectral analysis.
Conclusion: The results shows the high potential for the automatic detection of sleep stages and sleep apnea severity at the same time by analysis of heart rate variability. Since heart rate variability is a surrogate for autonomic activity this kind of detection will be limited to a rough discrimination of sleep stages and a rough discrimination of sleep apnea severity. The validity of the method in patients with disorders of the autonomic nervous system needs to be evaluated.

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Automated and Human Scoring of Sleep Stages in Normal Adults: A Comparison Study

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Introduction: Polysomnography(PSG) remains the gold standard for clinical and research evaluation of human sleep. Quantification of sleep stages and other biological signals rely upon human scoring. Uncertainty as to human-human variability of PSG scoring and limitations of standard scoring algorithms confound interpretation of results. Automated scoring may improve efficiency, reproducibility and cost of results, as well as expand data analysis. This study reviews an automated system, Morpheus I Sleep Scoring System.
Methods: Normal adults underwent standard PSG study of sleep, including 4 EEG, 2 EOG and EMG channels. 14 of 19 subjects with normal sleep history, normal physical exam and labs were evaluated and included. Ages ranged from 19 to 35 years. Sleep stages from digitized signals were manually scored by 3 RPSGT scorers with experience in both clinical and research scoring. Automatic scoring was performed with algorithms using adaptive segment analysis,fuzzy clustering and Markov models. Human supervision of automated scoring was also done and required less than 10 minutes per study. Manual scoring used Rechtschaffen and Kales rules. Study results were tabulated and inter-scorer comparison made by computing means +/- std. deviation. All scoring was blinded.
Results: All studies had acceptable signal quality for analysis. Automated, automated supervised (human edited), and three manual scored results of sleep architecture were as follows, respectively, in minutes: Sleep onset 8.0 +/- 9.0, 9.0 +/- 9.0, 9.2 +/- 8.8, 10.8 +/- 9.2, 17.2 +/-12.2; Latency to persistent sleep 16.1 +/-12.8, 17.3 +/-11.8, 17.7 +/-12.3, 19.4 +/-13.8, 17.8 +/-12.2; Total sleep time 449.8 +/-17.2, 450.0 +/-17.8, 434.5 +/-25.4, 430.2 +/-29.0, 432.8 +/-24.8; NREM 360.9 +/-28.9, 349.9 +/-24.5, 340.1 +/-24.5, 336.9 +/-24.3, 352.0 +/-21.6; REM 88.8 +/-27.3, 99.3 +/-25.3, 94.3 +/-21.1, 101.1 +/-23.7, 83.1 +/-29.9; REM latency 184.5 +/-72.3, 150.0 +/-55.5, 125.1 +/-52.2, 132.9 +/-77.1, 133.2 +/-49.7; WASO 22.3 +/-15.5, 21.4 +/-14.9, 29.2 +/-19.0, 31.8 +/-20.4, 29.8 +/-18.6; Wake 30.6 +/-17.3, 30.1 +/-17.4 38.3 +/-21.7, 41.9 +/-23.3, 40.4 +/-22.4; Delta 60.2 +/-17.8, 58.1 +/-16.5, 63.7 +/-35.4, 56.0 +/-23.8, 43.0 +/-23.5; Stage 1 40.8 +/-20.7, 35.6 +/-11.8, 43.0 +/-21.1, 27.5 +/-17.4, 53.0 +/-22.3; Stage 2 260.2 +/-12.9, 257.0 +/-15.5, 233.5 +/-28.5, 253.3 +/-32.4, 255.9 +/-21.3.
Conclusion: Automated scoring performed comparably to human scoring. Human supervision of automated scoring did not appreciably change study results except a small change in stage distribution and REM latency. In this study of normal adults automated scoring tended to have more sleep time. Advanced analyses by automated system were performed but could not be compared to human scoring.

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A Polysomnographic Method For Precise Evaluation Of Chemoreceptor Responses To Sleep Apnea In Infants

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Introduction: Polysomnographic recordings have gained justified recognition in diagnostic of sleep-disordered breathing, particularly OSA, arousal etc, due to a non-invasive character of the methods. In the present study we tested the applicability of breath by breath analysis of respiration in relation to changes in blood gases during breathing 4-6% CO2 for 6-8 min and 100% O2 for 1 min. The purpose was to test whether PSG recordings can be used for precise description of the chemoreceptor control of respiration in terms of response strength and reaction time.
Methods: Digital sleep recordings from infants were collected. The study population consisted of 112 infants (69 with apnoea of infancy (AOI) and 43 healthy controls). On the basis of the polysomnographic recordings, the AOI group was subdivided into two subgroups: (i) infants with periodic breathing and central apnoeas (PBCA, n=28), and (ii) infants with obstructive apnoeas (OA, n=41). The control group consisted of healthy infants who were born naturally, at term, after an uneventful pregnancy at the Karolinska Hospital. Infants were admitted to the laboratory at approximately 8 p.m., and settled to sleep supine and lightly dressed. No sedation or sleep deprivation was used. The respiratory movements of the chest and abdomen were recorded using inductance plethysmography integrated with a Monet Amplifier. For each breath, the following parameters were calculated: - sum of the amplitude of chest and abdominal movements, beat-to-beat R-R interval, SaO2 and pulse amplitude from toe pulse, skin TcPO2 and TcPO2 tensions and respiration rate. The hypercapnic and hyperoxic tests were performed during quiet sleep. CO2 test: after a 3 min breathing air control period, the gas flow (10l/min) was switched to 4%, and then to 6% CO2for 6-8 minutes, or until the infant moved or changed body position. The minimum duration of tests accepted for analysis was 6 minutes. O2 test: after the 1 min of air breathing control period, the inspiratory line was switched to 100% humidified oxygen for 60 seconds. Thereafter, the air breathing was re-established.
Results: The strength of the response was significantly greater in the control group compared with infants with PBCA and OA (291%/kPaCO2 and 41% and 130%/kPaCO2, respectively, p=0.002), and the response time was shortest in the control group (16 vs 64 and 54 breaths in the apnoea groups, p=0.002)1.
Conclusion: The present study highlights the mechanism of central control of respiration in the pathogenesis of apnoea of infancy. The study showed that data from detailed PSG recordings, based on the analyses of instantaneous, breath-by-breath changes, can be used in the exact quantification of strength and timing of ventilatory responses to CO2 and O2. Furthermore, the non-invasive character of the recordings makes the method fully applicable in clinical research of very sick infants.

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Identification of Bruxism in Treatment Seeking Patients and Controls

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Introduction: We have previously presented the BiteStrip bruxism device, a miniature, disposable electronic screener with EMG electrodes designed to identify masseter muscle contractions exceeding a predetermined individual threshold. BiteStrip scores were highly correlated with masseter EMG scored for bruxing events. Furthermore, unattended home use of the BiteStrip successfully distinguished "bruxers" from "non-bruxers", based on clinical referrals (bruxers) and history (non bruxers). In the present study, we compared BiteStrip scores in treatment-seeking individuals from a temoromandibular disorders (TMD) clinic with healthy college students with no orofacial complaints, to assess the clinical feasibility of the BiteStrip as a home screener for the identification of sleep bruxism.
Methods: 18 female patients seeking treatment at the Tel Aviv University TMD clinic (age (standard deviation): 28.7 (8.3)) and 17 female college students with no TMD complaints (age: 21.7 (1.9)), participated in the study. All underwent clinical examination by an orofacial pain expert. Patients were included if there was objective evidence of bruxism based on clinical oral examination, as well as subjective reports of audible grinding sounds by family member and/or complaints of morning symptoms such as masticatory muscles pain or fatigue. Control subjects had no objective clinical evidence of bruxism, and no subjective complaints. Participants used BiteStrips at home for 2 (controls) or 3 (patients) nights. Comparisons were made using the mean of nights per subject (meanscore) or the highest score for each subject (highscore).
Results: One patient was removed since she completed only one night with the BiteStrip. Average (and standard deviation) meanscores were 97.6 (56.2) and 42.7 (32.7), and highscores were 128.4 (56.4) and 68.0 (56.8) for patients and controls respectively. t-tests revealed significant differences for meanscore and highscore ($p<0.01$). Age was significantly different between the groups ($p<0.01$).
Conclusion: The BiteStrip is a useful screener, which may be used as a clinical aid for dentists to confirm or reject suspected bruxing activity during sleep. Age-matched data (including males) on a larger sample is currently being collected, and a multi center trial is underway, to establish BiteStrip score cutoff criteria and guidelines for home use.

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Temporal Features of Sleep Predict Hypertension: Application of a Novel Analysis of Sleep Stage Data From the Sleep Heart Health Study

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Introduction: Sleep Disordered Breathing (SDB) may contribute to the pathogenesis of hypertension (HTN) via vascular effects associated with intermittent hypoxemia and sleep disruption. Use of the apnea hypopnea index (AHI), hypoxic indices, or the arousal index, as exposure measures, however, has identified only modest associations with HTN. Limitations of traditional polysomnography (PSG) indices may relate to use of summary counts that provide little data on the temporal patterns of breathing and sleep changes. This study tested the utility of a novel analysis approach that describes the temporal patterns of sleep stage transitions relative to: 1. discriminating participants with and without HTN; and 2. predicting incident HTN.
Methods: Test sets for each aim were constructed by sampling data from Sleep Heart Health Study (SHHS) participants. For aim 1, data from 112 subjects < age 60 years without and 112 with HTN, were selected, frequency matched by age and sex. For aim 2, an independent set of 200 subjects who were non-HTNive at the baseline SHHS exam were selected, including 100 who developed HTN at approximately 5-year follow-up. Selection was independent of AHI. The analysis was based on scored sleep staging data obtained from 12-channel PSG. The approach used a

network model for sleep cycle patterns with the objective of revealing distinctive differences between the subjects in the time spent in each sleep stage and in the transitions between the stages. Data were analyzed using a novel network approach, the Fuzzy Measure Theoretic Quantum Approximation of an Abstract System (FMQAS), to obtain transitional measures between temporal sleep stages over the sleep record. Uncertainty measures are obtained for the transitional and sojourn times of the temporal sleep stages. These transition measures are aggregated and assessed relative to their discriminative and predictive properties. Each classification has an associated entropy value that provides a measure of the degree to which the participant belongs to each group.
Results: For aim 1, the median AHI was 9.9 and 11.0 events/hr for the non-HTN and HTN samples. The transition measures between Awake and Stage 3- 4 sleep correctly discriminated approximately 60% of the participants with and without HTN. The classification showed that the hypertensives were relatively more likely to transit between Awake and Stage 3-4. For aim 2, the baseline median AHI of subjects who remained non-hypertensive at SHHS follow-up was 7.6 compared to 8.3 for the group who developed HTN. The FMQAS measures, using data from the baseline SHHS exam, revealed that the transition measures between Awake and REM correctly predicted 5-year HTN incidence for approximately 60% of participants. A higher likelihood of transitions between Awake and REM were found in subjects who later developed incident HTN.
Conclusion: Although the models need to be confirmed in validation sets, they suggest that FMQAS-based description of the temporal sleep stage transitions may provide a powerful means for discriminating HTN status and for predicting incident HTN. Tools that robustly utilize the completely scored hypnogram may overcome previous limitations in the arousal index as a predictive index, and provide insight into the role of sleep-associated disturbances in vascular disease.

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Nocturnal Finger Arterial Tonometry And Its Relation To Daytime Blood Pressure And The Presence Of Hypertension

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Introduction: Arousal from sleep causes immediate fluctuations of autonomic activity and blood pressure. The association between these nocturnal fluctuations and daytime blood pressure is unknown. Finger arterial tonometry is a tool to assess overnight changes in pulse wave amplitude (PWA) in the finger vascular bed. Phenomena like arousal, sleep stage, and ambient temperature cause profound changes in PWA. This study systematically analysed the association between nocturnal PWA changes and daytime blood pressure in a population based cohort enriched with hypertensive patients.
Methods: SUBJECTS: A case control analysis was undertaken in ninety-eight subjects (55 males, mean age 60±7 yrs, mean BMI 28±4 kg/m2, hypertensives (n=21)), randomly selected and consecutively surveyed in the Skaraborg Hypertension Project. METHODS: Subjects underwent simultaneous unattended-home polysomnography (PSG) and finger arterial tonometry (Watch_PAT 100). The PAT recordings were automatically analysed for attenuation of the PWA (PWA classes 5-70% attenuation). PSG recordings were manually scored for respiratory, motor and unspecific arousals according to international criteria.
Results: There was a substantial correlation between the number of 45% PWA attenuations and mean as well as diastolic daytime blood pressures in all subjects (ANOVA, p=0.020 and 0.039, respectively). PWA attenuations in the 35 to 55% range were equally or more closely related with daytime blood pressure (p between 0.1 and <0.01) than traditional PSG parameters of sleep fragmentation. Subgroup analysis revealed that PAT values correlated more strongly with diastolic blood pressure in patients with sleep related breathing disorder (SRBD) (55% PWA attenuation class, r=0.37, p=0.01) while systolic blood pressure was better predicted in subjects without SRBD (45% PWA attenuation class, r=0.32, p=0.028). Presence of systemic hypertension was positively correlated with the number of PWA attenuations.
Conclusion: This is the first report to demonstrate that frequency and degree of PWA attenuation, obtained by finger arterial tonometry, is associated with daytime blood pressure and presence of hypertension. This novel approach suggests that continuous monitoring of finger PWA may be used for identification of cardiovascular disease.

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What Is the Incremental Contribution of Various Sensors to Estimation of the Apnea Hypopnea Index?

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Introduction: Increasingly advanced technology continues to be developed for screening and diagnosing patients with obstructive sleep apnea (OSA). Monitoring options include flexibility to choose from a wide range of sensors and data processing algorithms to quantify the apnea hypopnea index (AHI) and associated sleep measures. Although attempts have been made to standardize approaches for measurement and scoring, most recommendations have not been fully evidenced-based. The results of alternative approaches for scoring the AHI, the most common metric used for OSA screening and diagnosis, are unclear. This study aims to quantify the associations among AHIs based on varying combinations of signals, comparing each to the gold standard 12-channel montage. Specific interest was in the impact of newer sensors, such as the nasal pressure cannula, as well as the influence of sleep staging data, on AHI determination.
Methods: 30 polysomnographic (PSG) studies, representing a range of severity for OSA, were randomly identified from a research database. Each overnight in-hospital PSG included recordings of two central EEGs, bilateral EOGs, a bipolar submental EMG, thoracic and abdominal respiratory inductance plethysmography (IP), nasal-oral thermistry, flow from a nasal pressure recording, finger pulse oximetry, electrocardiogram (ECG), body position, and bilateral leg movements with piezo sensors (Compumedics E Series, Abbotsville, AU). Each study was re-scored using 9 different montages, displaying varying combinations of signals: oximetry only (Montage 1, M1); oximetry and ECG (M2); oximetry, IP, ECG (M3); M3 plus nasal flow (M4); M3 plus thermistry (M5); M3 plus thermistry and nasal flow (M6); a full montage other than leg movements (M7); a full montage, but scoring respiratory and sleep staging data independently (in "2-passes") (M8); and a full montage, scored with all channels visualized together (M9). Scoring was performed by a team of 5 certified research polysomnologists blinded to the results of previous scoring. Specific scoring approaches for identifying respiratory events for each montage were determined prior to re-scoring. Levels of agreement among the AHIs from each montage were assessed using the intraclass correlation coefficient (ICC) (for the log-transformed AHI) and the kappa statistic (for categorical outcomes: AHI 0 to

<5; 5 to <30, and > 30).
Results: The mean AHI for the gold standard M9 montage was 24.9. Respective mean AHIs (and differences relative to the gold standard M9) derived from each montage were: 24.1 (0.8), 22.9 (2.0), 24.1 (0.8), 23.0 (1.9), 22.7 (2.2), 23.5 (1.4), 24.6 (0.3), 24.8 (0.0), for montages 1-8, respectively. The ICCs for each of the M1 to M8 montages, relative to the gold standard, varied from 0.94 (0.87-0.97, 95% C.I.) for M1, to 0.99 (0.97-0.99) for M3. Similarly, the kappa statistics, quantifying the level of agreement among clinically relevant categories of AHI for the gold standard as compared to the other 8 montages, varied from 0.82 (0.66-0.97) for M1 to 1.0 for M3.
Conclusion: These data indicate that highly accurate estimates of the AHI can be derived from any combination of commonly used channels, provided that data are scored using well-defined, standardized algorithms.

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Sleep Estimation With Wrist Actigraphy: A Comparison of Three Data Modes in Adolescents With And Without Sleep Disordered Breathing

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Introduction: The importance of measuring sleep in adolescence, a time of rapid changes in sleep habits and rising prevalence of sleepiness, is increasingly recognized. Among the tools for measuring sleep time and quality is wrist actigraphy, a non-invasive means of estimating sleep based on recording motion data. In adults, actigraphy-based measurements of sleep correlate well with sleep data obtained from EEG recordings obtained with polysomnography (PSG). Since the association between movement and sleep may vary with age, the technically optimal approach to data acquisition and analysis may also need to vary across the age spectrum. The analog signal generated by movement can be digitized and analyzed using one of three data modes, Zero-Crossing (ZCM), Time-Above-Threshold (TAT), and Proportional-Integration-Mode (PIM). Although ZCM is most often used in studies of sleep, there are little data to justify its use in specific age groups. This analysis tests the hypothesis that wrist actigraphy correlates well with PSG in adolescents, and attempts to identify the data mode that best correlates with PSG-determined sleep estimates in this age group.
Methods: Fifty adolescents between the ages of 13-18 years from a non-clinical community-based cohort (92%) and from clinical referrals (8%) were concurrently monitored with PSG and wrist actigraphy using all three data modes to measure total sleep time (TST). Actigraphy data were collected using Octagonal Sleep Watch 2.01 (AMI, Ambulatory Monitoring, Inc., Ardsley, NY) and scored with Action-W software (AMI). The apnea hypopnea index (AHI) was defined as total number of obstructive apneas and the number of hypopneas associated with >= 3% oxygen desaturation per hour of sleep. Those with either an AHI >= 5 or with reported habitual loud snoring were classified as having sleep disordered breathing (SDB).
Results: The sample was 46% male, 14% with an AHI >=5, and 28% with SDB. Intraclass Correlations (ICC) between actigraphy and PSG for TST were generally low to modest, and were highest for TAT (0.30) compared to ZCM (0.23) and PIM (0.24). Subgroup analyses revealed that the highest ICCs were among those without SDB (TAT=0.60, ZCM=0.43, PIM=0.41). ICCs for all 3 data modes were close to 0 among adolescents with SDB.
Conclusion: The correlations for TST from wrist actigraphy and PSG suggest that actigraphy provides a reasonable estimate of sleep in adolescents without SDB. Estimates of sleep based on movement in adolescents with SDB appear less reliable, possibly because of limitations in motion-based algorithms to accurately classify sleep time in the presence of SDB-associated movement arousals. Of the three data modes, TAT estimates of sleep time showed the highest correlation with PSG sleep time. Recognition of the variation in sleep estimates among different data collection modes, between population sub-groups, and across the age spectrum, may be of fundamental importance in the interpretation of actigraphy data for sleep estimation.

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A Novel Neonatal Telemetry System for Sleep Monitoring

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Introduction: The project objective was to illustrate that a novel, practical, and inexpensive means of monitoring the physiological and behavioral state of neonates during sleep provided the same information as a traditional cart-mounted monitoring unit. These traditional, cart-mounted bedside units, at present are large and cumbersome, which impede nursing care and inhibit the clinical traffic around the infant in an isolette in a busy neonatal intensive care unit. Innovative methods for assessing brain function, therefore, are needed that can take advantage of technological advances to accommodate the unique needs of the high-risk neonatal patient in a neonatal intensive care setting.
Methods: A novel, untethered system for monitoring sleep, the Crystal Monitor® Model 16, was developed to record and transmit physiological data to a laptop computer located up to 200 feet away. This small (4.0 x 2.2 x 0.7 inches), lightweight (3.8 oz) system was evaluated in a side-by-side comparison to a traditional cart mounted, Nihon Kohden system. Physiological data was recorded from seventy neonatal subjects in the neonatal intensive care unit of University Hospitals of Cleveland. All neonates were between 31 and 33 weeks post conceptional age. Using the same recording electrodes, data was simultaneously recorded with both the novel and traditional systems. Six channels of electroencephalography (EEG) and two channels of electro-oculography (EOG) were collected for each neonatal subject. Each sleep study lasted approximately three hours. EEG recording sites included T3, C3, T4, C4, O1, and O2. Collected data from each system was scored by a clinician for EEG sleep state. Presence of trace discontinu indicates quiet sleep state in neonatal subjects whereas continuous EEG indicates active sleep. The clinician was blinded to the system and patient during scoring of EEG sleep state. The inter-system reliability between the traditional and novel system was computed by calculating Cohens Kappa scores.
Results: To this point, scoring has been completed on fourteen of the seventy collected data files. The inter-system reliability Kappa score for EEG sleep state was 82.1% (average 58.8 minutes per subject). These results indicate that the correlation between the scores produced by the novel and traditional systems were similar. In addition to the quantitative scores, the novel untethered system provided less obtrusive monitoring than the traditional cart mounted system. The miniature system required substantially less space in the neonatal intensive care unit than the cart mounted system.
Conclusion: The novel wireless neonatal monitoring system provided EEG state scores comparable to the traditional cart mounted system. This miniaturized bedside EEG and sleep monitor may greatly enhance

clinicians abilities to diagnose and therapeutically intervene for specific forms of neonatal brain disorders.

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The Relationship Between Actigraphy and Polysomnography in Healthy Children and Adolescents

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Introduction: Although several studies have assessed the relationship between actigraphy and sleep laboratory data, few have evaluated the potential influence of age and gender on these measures. The primary aim of this study was to determine how the relationship between standard polysomnographic and actigraphic measures differed between children and adolescents and if the age-related differences interacted with gender.
Methods: 30 (15M, 15F) healthy children and adolescents, 8-18 years of age, participated in the study. All underwent medical and psychiatric evaluation to determine eligibility to participate. The sample was free of personal or family history of psychopathy, and was medically fit. Medication, caffeine and alcohol were proscribed for the duration of study. Participants maintained regularized sleep wake schedules for 5 days prior to spend the night in the sleep laboratory. Each participant wore an actiwatchR (MiniMitter) during home recordings and on sleep laboratory nights. Visual stage scoring was conducted according to standard criteria. Lights on and lights off times from the actiwatch were synchronized with the polysomnogram (PSG). Sleep latency, total sleep time, sleep efficiency and number of awakenings were the key focus of the analyses. ANOVA evaluated age by gender main effects and interactions on the difference between comparable PSG and actigraphy measures. Correlations between the two sets of measures were also computed, separately by gender.
Results: With the exception of young girls (<12 years of age), agreement between actigraphy and polysomnography was high for sleep efficiency. Sleep efficiency was about 6% higher from polysomnography in young girls with less than 2% difference in all other groups. Actigraphy overestimated sleep latency in young girls, but not adolescent girls (13-18), and consistently underestimated sleep latency in boys, regardless of age. In examining the raw data, it was clear that the actigraphy was particularly sensitive to small movements in young girls that were not intrusive enough to impact on visual stage scores. The largest difference between polysomnography and actigraphy was for total sleep time, also found in the young girls. Total sleep time was underestimated by nearly 30 minutes with actigraphy compared to 6 minutes less total sleep time in young boys. By contrast total sleep time in the adolescents girls differed only by 1.3 minutes. Actigraphy overestimated total sleep time by 5.8 minutes in adolescent boys. ANOVA revealed a significant age by gender interaction and an age main effect for total sleep time, but not for any other variables ($p<.03$). Correlations between PSG and actigraphy measures of total sleep time and sleep latency were higher for males than for females, collapsed across age. However, age was more strongly correlated with PSG and actigraphy measures in the females.
Conclusion: In general, there was good agreement between actigraphic and PSG measures of sleep in children and adolescents, although agreement between the two sets of measures was better among adolescents. However, the influence of age on the relationship between actigraphy and PSG measures was strongly influenced by gender. These findings support previous work suggesting that age-related changes in sleep differ for males and females.

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Innovative Wireless Sleep Apnea Monitoring System

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Introduction: Estimates from the 1990 census conclude that there are 25,130,470 men and women in the U. S. with untreated, undiagnosed obstructive sleep apnea. The Crystal Monitor® 16-S developed by Cleveland Medical Devices is an 11-channel monitor system that for sleep apnea diagnosis. This innovative monitor is wireless facilitating setup in any hospital or clinic room permitting sleep monitoring on patients who may not be capable of transport to a sleep lab. The system includes a patient unit, computer unit and PocketPSGTM software. The system provides real-time data display and scoring and flexible report generation capability. The patient unit (transmitter) weighs 200g and measures 4.5" x 2.5" x 1". The computer unit (receiver) weighs 90g and measures 3.5" x 2" x 1". The patient unit is battery powered and can last at least twelve hours of continuous use. The system acquires eleven channels: C3-A2, O2-A1, LOC-ROC, ECG, Chin EMG, Pulse Oximetry, Airflow, Snore, Chest and abdominal respiratory efforts and Body position. The airflow signal is detected with a pressure transducer housed inside the monitor. Special algorithms derive snore from the airflow cannula, so no additional snore sensor is needed.
Methods: Side-by-side clinical comparison between the wireless monitor and Respironics Alice 4 system was done. Both systems were simultaneously connected to the subject for one night. A total of 4 subjects referred for PSG studies were enrolled in the study. Several channels used the same electrodes and sensors, and were connected to both systems via a Y connection at the head box. The remaining channels were added to the patient's hookup. Recordings from both systems were scored by the same sleep technologist. Scoring included sleep staging, arousals, hypopneas, and apneas. All of the recordings were of good quality. The leads stayed in place for the duration of the night allowing all channels to be scored completely. An average of 30 seconds was lost using the wireless monitor over the entire recording period.
Results: Sleep staging was similar in both systems. Maximum variation was seen in stage 2 with the traditional system scoring an average of 7% longer duration in stage 2 than the wireless monitor. Apnea detection was also similar with the maximum difference of 8. This is comparable to the intra-scorer variability seen in previous research on a single scoring system. The wireless monitor showed two of four patients significantly higher AHI (AHI=14, 8 vs. AHI=3, 1)with the largest variation showing a threefold increase. Higher AHI in the wireless system can be attributed to the pressure-based airflow technique which is more sensitive to breathing fluctuations than the traditional thermistor.
Conclusion: The wireless system generated results that were comparable to the traditional system in sleep structure evaluation. and apnea detection. However, the wireless monitor was more sensitive to apneas and hypopneas, which can be explained by differences in airflow measurement techniques. Overall, this preliminary study shows the potential viability of this new wireless system as an accurate way to monitor sleep apnea in traditional and non-traditional attended settings such as nursing homes and rural hospitals.

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A Limited-Channel Single-Site System to Diagnose Obstructive Sleep Apnea (OSA): Comparison of Full Polysomnography (PSG) with In-home and In-Lab Recordings

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Introduction: An apnea risk evaluation system (ARES) was evaluated during both laboratory and in-home use. The ARES uses a multivariate approach that integrates: a self-applied, single-site (forehead) device to acquire continuous full-disclosure physiological signals (i.e., forehead pulse-oximetry (SpO2), pulse rate, snoring sounds, head movement and head position); a validated questionnaire based on anthropomorphic and clinical information; automated software to recognize and quantify abnormal respiratory events; and an expert system which utilizes this information to identify levels of severity.

Methods: Laboratory-PSG and simultaneous ARES recordings were acquired from 198 subjects. Subjects wore the ARES in-home for two nights prior or subsequent to their PSG (based on random assignment). Fifteen patient records were dropped; seven due to study length (minimum: lab >1.5-hours, in-home >6-hours), eight due to poor quality data (PSG=6, ARES=2), leaving 173 records for analysis. The population included 129 patients referred for PSG, and 16 subjects classified as at-risk and 28 no-risk based on the ARES-questionnaire analysis. The PSG Apnea-Hypopnea Index (PSG-AHI) was based on AASM guidelines for detection of obstructive and central apneas/hypopneas, modified to require a minimum 3% rather than a 4% SpO2 desaturation. A diagnostic cut-off of AHI=10 was used to establish the accuracy and validity of the ARES. Calculation of the ARES respiratory disturbance index (ARES-RDI) was based on minimum SpO2 desaturation and resaturation requirements that varied depending on the SpO2 level at the point of maximum saturation, (e.g., >93.0%=2.5%-2.5%, 92.9%-91.5%=3.0%-2.7%, 91.4-88%=3.5%-3.0%, <88%=4.0%-3.2%) with moderate vs. severe obstructive events determined by the slope of resaturation. When maximum saturations were >95%, events with 2.2% desaturation and resaturation were included if accompanied by head movement and/or heart rate arousals.

Results: The PSG-AHI was significantly correlated with both in-lab ARES-RDI (r =0.96) and in-home ARES-RDI (r =0.88). The best-fit line for the lab results (y=3.9+0.92x) showed the ARES-RDI consistently greater across all PSG-AHI ranges (0-117 events/hour). The best-fit line for the in-home results (y=6.2+0.70x) showed the ARES-RDI greater until PSG-AHI=27 and then lower. Bland-Altman plots show a tight distribution of the differences between the ARES-RDI and PSG-AHI plotted around the mean (AHI+RDI/2) for both lab (mean=1.7 + 7.1 events/hour) and in-home (mean= -2.3 + 14.5 events/hour) results. The sensitivity and specificity for the lab-ARES, compared to PSG with a diagnostic cut-off of 10, was 96% and 86%. The negative and positive predictive values were 92% and 94%. For the in-home ARES, the sensitivity and specificity was 91% and 85%. The negative and positive predictive values were 91% and 85%. Five of the 10 false-positive in-home ARES results were classified as false-positives by the lab-ARES. Of the 10 false-negative in-home ARES, seven were identified as at-risk by the ARES questionnaire analysis.

Conclusion: The ARES demonstrated consistently high specificity for both lab and in-home recordings. The in-home sensitivity was slightly lower than in the lab, and may be explained in-home vs in-lab variability. In persons with possible OSA who a priori do not require an attended study, the ARES could be part of a low-cost alternative-management strategy.

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Interscorer Reliability Of Scoring Sleep Studies (Staging, Respiratory Events And Arousals) In Patients With Different Severity Of Sleep Disordered Breathing

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Introduction: Introduction: Routine assessment of interscorer reliability is both an AASM accreditation requirement, and an important exercise for improving scoring rules. Interscorer reliability can be influenced by type of patient (normal, patients with Sleep Disordered Breathing (SDB), insomnia etc), level of sleep fragmentation and scorer's characteristics (represent same or different centers). Reliability of scoring for respiratory disturbances and sleep staging has been demonstrated in the research setting using large datasets (e.g Sleep Heart Health Study). Implementing these techniques in a routine clinical setting has not been commonly done. Thus this report evaluates interscorer agreement in patients with different severity of SDB based on staging, respiratory events and arousals in a large clinical practice group.

Methods: Methods: Four board certified (RPSGT) experienced scorers were selected from 1 full-time scoring team (12 scorers, SLEEPTECH, Inc.) and each blindly scored overnight sleep (PSG) studies performed in the previous 3-month period. The RPSGT's were asked to score the records as part of routine monthly quality assurance, and none of the scorers was aware of the study aims. All records were from patients referred for evaluation of SDB. The PSG's were assigned to one of the following groups: 1) AHI<10; 2) 10<AHI<20; 3) AHI>40. All scorers used R&K scoring rules for staging and arousals and Medicare criteria for respiratory events (hypopneas required desaturations > 4% with accompanying arousal). Scorer agreement on epoch-by-epoch sleep staging was evaluated using the kappa statistic and intraclass coefficients (ICC) for interscorer reliability of respiratory disturbance and arousal indices.

Results: Results: There were 5 PSG's scored in each of the 3 groups (total of 15 PSG's, all patients were male). The mean age (years), BMI (kg/m2) and RDI (#/hr) respectively for the 3 groups were: Group 1-38.6, 29.2, 3.3; Group 2 - 44.2, 31.2, 18.0; and Group 3 - 49.0, 32.6, 60.8. Overall Kappa scores for the 6 interscorer pairs ranged from 0.75 to 0.80. These values were highest in Group 2 (0.78-0.84) and lowest in the Group 3 (0.72-0.78). Of a total of 12,305 epochs scored, the percent agreement between scorers was 84-88%. ICC's for RDI ranged from 0.83 to 0.97 and for Arousal index from 0.52-0.88. The Highest ICC's were in the group with the highest RDI.

Conclusion: Conclusions: High interscorer reliability can be obtained in a routine clinical setting. Monitoring the results of regular interrater scoring can ensure the highest quality in diagnostic sleep testing.

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Validation of an Automatic Sleep Scoring Program Using Neural Network

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Introduction: Visual sleep scoring is a laborious and time-consuming process. It was the only method of quantifying sleep states from paper

polygraph records, and remains a standard procedure for sleep studies. With the wide availability of powerful computers, manual sleep scoring has become a bottleneck for sleep analysis, especially in long-term studies. We have developed an automatic scoring routine that trains a neural network to associate EEG and EMG features of individual sleep stages with a human expert's visual scores. It then performs automated scoring of novel sleep data with a degree of reliability comparable to human visual scoring. This study was done to validate the method by comparing visual scores and automatic scores of sleep data from six rhesus monkeys.

Methods: An automated scoring program was developed in Matlab 5 (Mathworks Inc., Natick, MA). A three-layer neural network model was constructed consisting of: 25 neurons in an input layer corresponding to specific features in the EEG/EMG pattern; 4 neurons in a hidden layer; and 4 neurons in an output layer corresponding to four sleep stages (Wake, REM, S12, S34) in rhesus monkeys. In the training phase, the program computes an error function between the network output and an expert's visual scores. Network weights are then adjusted to reduce the error function by the back-propagation algorithm. A typical training session consists of 4000 feedback iterations on 1920 to 2640 epochs (16 to 22 h of recording), and requires about 1.5 hours of computation on a 500 MHz PowerMac G4. Once the network is trained, novel data are scored in a single pass consisting of data input, feature extraction, and network-output steps. In this study, the program was trained using data from six animals in separate sessions. Two days of novel data from each animal were then scored by the automatic scoring program as well as by two human scorers.

Results: The scores of 34,374 epochs of sleep recording were compared. The overall agreement between the two human scorers (H-H) was on average 92.3%, while the agreement between automatic scoring and human scoring (H-A) averaged 93.7%. REM sleep showed the lowest agreement, averaging only 82.0% for H-H and 84.9% for H-A. When only the visual scores on which human scorers agreed were considered, the overall agreement between automatic scores and human scores improved to 97.5%. Agreement on REM sleep improved as well, reaching 91.8% on average. When sleep stages S12 and S34 are combined as NREM, the overall agreement improves further (94.4% H-H, 95.4% H-A, and 98.1% HC-A).

Conclusion: The results strongly support the use of neural networks in automatic sleep scoring as a reliable and effective alternative to human visual sleep scoring in rhesus monkeys. This method can be easily applied to sleep scoring in rodents or other animals as well.

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Neural Net Based Arrhythmia Analysis Software

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Introduction: A new, innovative, neural-based analysis software, capable of accurately detecting heart rate variability and many cardiac arrhythmias for the sleep specialist, was developed and tested. Many studies have shown a strong link between cardiovascular disease and sleep disorders. Therefore, it is important for sleep monitors to accurately detect cardiac events during Polysomnography to identify those patients who need to be referred to a cardiologist for further diagnosis. The newly developed CleveMed heartbeat and arrhythmia analysis software is designed to analyze electrocardiogram (ECG) signals, calculate the heartbeat and detect heartbeat arrhythmia. The software consists of a wave analysis section, to detect the waveform specifics and heartbeat, and a neural network based section, to classify the arrhythmia. We found the wave analysis section to have a 98.7% accuracy and the neural network based section to have greater than a 96% success.

Methods: The MIT-BIH Arrhythmia Database, a collection of 48 ECG recordings, containing over 110,000 heartbeats and annotations, was used to validate the wave analysis software (WAS). The WAS was matched to an annotation from the database, if the heartbeat detected by the algorithm was within a few sample numbers of the database annotation. The number of matches was used as a measure of how well the WAS correctly identified heartbeats. Subsequently, the detected heartbeats were used as inputs for the arrhythmia detection neural network (ADNN). The ADNN uses 13 waveform specific inputs to classify each heartbeat into an arrhythmia group. The ADNN then outputs classification groups associated with one or more particular arrhythmias. Ideally, each classification would have a 100% association with a single arrhythmia (or normal).

Results: The ADNN identified normal, left and right bundle branch block, atrial, aberrated atrial, nodal and supraventricular premature, ventricular contraction, atrial, nodal and ventricular escape beat, and non-conducted P-wave types of heartbeats. We found the wave analysis section to have a 98.7% accuracy and the neural network based section to have greater than a 96% success. Of the 5,512 annotations from the database without a heartbeat detected by the WAS, 960 were excluded as lead in and lead out phases, and another 2,316 were comments (not heartbeats). The remaining 2,236 annotations (2.1%) were genuine misses. Two typical errors conditions include when there is no identifiable heartbeat pattern (wild, random signals) and when a heartbeat borders on being normal (upward) or inverted (downward). The ADNN created 7,117 clusters of heartbeats. 5,866 of the clusters were 100% correlated to one type of heartbeat. The 1,251 non-100% correlated clusters consisted of 4,233 heartbeats. Therefore, the ADNN correlated over 96% of the heartbeats with 100% confidence.

Conclusion: A new heartbeat and arrhythmia analysis software was developed. The software includes a wave analysis section to detect the heartbeat waveform and a neural network based section to classify the arrhythmia. This analysis software promises to generate an accurate heart rate variability and cardiac arrhythmia detector. Future work will include additional testing and further neural network training.

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A New Single-Item Sleep Quality Scale: Validation Results in Chronic Primary Insomnia and Depressed Patients

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Introduction: Long or frequently administered self-reported sleep questionnaires may not be feasible in some clinical trials. Therefore, a single-item, self-rated, global sleep quality assessment called the Sleep Quality Scale (SQS) was developed. Overall sleep quality over a seven-day recall period is evaluated by marking an integer score from 0 to 10, with the following anchors: 0=terrible, 1-3=poor; 4-6=fair; 7-9=good; and 10=excellent. In the instructions, respondents are asked to consider core components of sleep quality such as: how many hours of sleep they had, how easily they fell asleep, how often they woke up during the night, how often they woke up earlier than they had to in the morning, and how refreshing their sleep was.

Methods: Measurement characteristics of the SQS relative to validated, widely-used sleep questionnaires (i.e., the Morning Questionnaire (MQI) administered daily and the Pittsburgh Sleep Quality Index (PSQI) with one-week recall) were assessed according to a pre-specified validation analysis plan using two study populations: 1) patients with chronic primary insomnia and 2) patients with major depressive disorder. Data

for the insomnia population were obtained from a study with a one-week washout period followed by 4 weeks of usual care with an FDA-approved hypnotic. Data for the depressed population were obtained from a study of an antidepressant treatment during which patients received active or experimental therapy for eight weeks following a one-week washout period.
Results: For the insomnia population (n=70), concurrent criterion validity of the SQS relative to average MQI Sleep Quality (Item 8) for Week 1 was -0.76 (Pearson correlation), four-week test-retest reliability during a stable period of treatment was 0.62 (intraclass correlation coefficient), and effect size was 1.32 (standardized response mean for change from baseline to Week 1). For the depressed population (n=651), concurrent criterion validity relative to PSQI Sleep Quality (Item 6) at Week 8 was -0.92 (Goodman-Kruskal correlation), one-week test-retest reliability in stable patients was 0.74 (intraclass correlation coefficient), and effect size was 0.67 (standardized response mean for change from baseline to Week 8). The Pearson correlation between the SQS and PSQI global score at Week 8 was -0.72 in depressed patients, and correlations between the SQS and core components of sleep quality were stronger than those with other PSQI items/component scores. Mean SQS scores of 7.5, 5.9, and 3.5 were observed at Week 8 for depressed patients categorized as Normal, Borderline, and Problem Sleepers (defined by PSQI global scores of <5, 5-8, and >8 (Carpenter and Andrykowski, 1988)). Mean changes in SQS from baseline to Week 8 were 4.9, 2.6, 0.5, -1.2, and -3.3 in depressed patients categorized as: Greatly Improved (-2 to-3), Somewhat Improved (-1), No Change (0), Somewhat Worsened (+1), and Greatly Worsened (+2 to +3) with respect to PSQI Sleep Quality (Item 6).
Conclusion: The Sleep Quality Scale (SQS) possesses favorable measurement characteristics (i.e., strong concurrent criterion, convergent, divergent, and known-groups validity, effect size, and adequate test retest reliability) relative to more frequently administered and/or lengthy, validated, self-rated sleep questionnaires.

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Validating an Empirical Continuous Positive Airway Pressure Equation

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Introduction: Previous studies have endorsed a prediction equation for the determination of an optimal level of continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnea. The equation utilized a combination of anthropometric measurements (body mass index (BMI) and neck circumference (NC)), and the apnea/hypopnea index (AHI) to predict optimal CPAP pressure. The purpose of this investigation was to demonstrate that this equation would be unsuccessful in predicting accurate CPAP pressure.
Methods: We retrospectively recruited participants that underwent a polysomnogram (PSG) recording at our facility, a tertiary referral center, and had available anthropometric measurements. Our sample included participants that required CPAP treatment (n=38), and those who did not as determined through physician evaluation of the diagnostic PSG (n= 31). To avoid gender bias, a similar proportion of males (n= 35) and females (n= 34) were recruited. If patients were titrated on CPAP, their optimal pressure was designated as the Actual Pressure (AP); for patients who did not require CPAP their AP = 0. The Predicted Pressure (PP) was calculated for all participants utilizing the following equation: PP = (0.16 × BMI) + (0.13 × NC) + (0.04 × AHI) - 5.12. To study the AP and PP the paired t-test was used to compare mean values. Correlation analysis was utilized to evaluate the relationship among AP and PP within the entire sample, as well as exclusively among the participants that required CPAP.
Results: Our population consisted of obese (mean BMI= 37.1 ± 9.2), middle aged participants (mean AGE= 51.3 ± 10.9) with severe sleep apnea (mean AHI= 26.4 ± 33.9). There was a significant difference between AP and PP among all participants ($p < 0.01$); both variables were correlated ($r = 0.607$, $p < 0.01$). The PP accurately predicted CPAP pressure 7% of the time, and under/over- predicted the pressure 37% and 57% respectively. With a broader definition of PP, within ±2.0 cm H2O of AP, the PP accurately predicted CPAP pressure in 26%, and under/over-predicted pressures in 23% and 51% of participants respectively. When the participants with CPAP titrations were isolated, a significant difference was observed among AP and PP, and the variables were poorly correlated ($r = 0.214$, $p < 0.003$). Among participants who did not require CPAP, the CPAP pressure was overestimated 100% of time (Range= 9.0 cm H2O).
Conclusion: Predictive CPAP equations have been developed with the aim of shortening CPAP titration time, and to serve as the best "educated guess" of CPAP pressure prior to an in-laboratory diagnosis. The proposed equation adequately predicted AP, or within ±2.0 cm H2O of the AP, in 7% and 26% of our total participants respectively. Within our population, the equation over-predicted the CPAP pressure in 50-60% of participants which may result in reduced CPAP compliance and increased sleep fragmentation. Also, among participants that did not require CPAP (mean AHI= 5.0 ± 4.9), the predictive equation misdiagnosed 100% of the time. Based upon our investigation we hold that the predictive equation fails to serve as an adequate replacement of in-laboratory CPAP titrations.

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Automated Sleep-Stage Scoring Using a Support Vector Machine

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Introduction: Sleep research studies evaluate various stages of sleep in animals and humans alike by evaluating polygraphic information about the test subject. Traditionally, polygraphic sleep records have been scored manually. Such a system of scoring is tedious, time consuming, inefficient, and prone to human error. Support vector machines (SVMs) are a class of machine learning methods that have been proven to be superior to other approaches for a variety of biomedical applications. An automated scoring system based on an SVM was chosen for this study to differentiate between vigilance states of waking, paradoxical sleep (PS), and high voltage sleep (HS) in rodents.
Methods: Retrospective data from three Sprague-Dawley rodents consisting of 12 hours of scored sleep each were used for this study. Data collected from three bipolar electrode channels comprised the recording from each rodent. The electrodes measure activity on the parietal cortex, the temporalis muscle, and the hippocampal theta activity on the parietal cortex. Recorded signals were low-pass filtered at 90 Hz and converted from analog to digital signals. Frequency and time domain features that previous studies have deemed to be useful were extracted from each 20-second epoch using MATLAB (Mathworks, Inc.). An optimal features subset was determined through the analysis of variance test (ANOVA) and the visual t-test. An SVM was designed in MATLAB to automate the sleep scoring process. The SVM was trained using two hour's worth of data manually scored by two experts. Extracted features were normalized and processed with kernel functions that perform a non-linear mapping into a higher dimensional feature space, where the data were separated by optimal hyperplanes. All parameters of the SVM, including the feature set, kernel function, and various constants, were optimized based on the training data. The remaining hours were then automatically scored and compared to the manual scores of both experts through a sta-

tistical analysis involving calculations of percent agreement.
Results: Frequency and time domain features were selected for the feature set if the visual t-test indicated a significant difference between at least two stages of sleep and the p-value of the ANOVA test was below 0.05 for all sleep files evaluated. Various kernel functions were examined and a Gaussian radial basis function was selected as optimal. The SVM results were relatively insensitive to changes in the width of the radial basis function although the soft-margin upper-bound parameter improved results as it was decreased from infinity to unity. Using the optimal parameters the overall percent agreement for both experts was above 92%
Conclusion: An automated scoring system was developed to discriminate among waking, high voltage sleep, and paradoxical sleep. The program extracts the useful features and implements the features into a SVM for automatic classification. The SVM design is optimized in terms of kernel function, features, and constants so as to obtain optimal results. The system reduces the time needed to score sleep, is less tedious, and provides objective scoring. Based on the agreement with experts, this study demonstrates the value of SVMs in effectively and automatically classifying rodent sleep stages.

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Novel Computerized EEG Algorithms for High Resolution Characterization of Wake-Sleep Transitions

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Introduction: More accurate and high temporal resolution characterization of wake-sleep states using computerized EEG analysis will address the strong need of both research and clinical sleep communities to better quantify the transitions between wakefulness and sleep. For example, a better characterization of the profile of this transition will have far reaching implications in quantifying sleepiness whose assessment is primarily based on detection of onset of sleep. On the other hand, short-duration disruptions to sleep resulting in micro-arousals can also benefit from these sophisticated signal processing methods. We have developed and clinically validated a novel class of algorithms that are capable of automatic high resolution detection of micro-sleeps and micro-arousals using a single EEG electrode.
Methods: The new class of algorithms is based on an innovative combination and simultaneous real-time utilization of several major signal processing methods for quantifying EEG, including traditional Short-Term Fourier Transform, Recursive autoregressive parameter estimation, and Wavelet analysis. Thus, each method is utilized for its particular strength in producing time-varying indices that best characterizes the time/frequency spectral content of EEG signal. The novel algorithms were embedded in a software package in Matlab programming language for analyzing PSG data.
Results: We utilized these techniques for automatic detection of sleep onset in 80 naps from 20 patients undergoing their routine clinical test of sleepiness, MSLT (Multiple Sleep Latency Test). The sleep onset that was automatically detected by our automatic algorithms using a single EEG channel highly correlated (Corr. Coeff > 95%) with the sleep onset times determined by experienced registered PSG technologist (who utilize all of the EEG, EOG (eye movement), and chin EMG channels available during MSLT to determine sleep onset.) Linear Regression between the two sets of data produced an intercept of 52 seconds, suggesting that our method can potentially detect onset about a minute earlier than the standard R&K criteria (used for scoring MSLT).
Conclusion: Our new class of algorithms performed well in detecting sleep onset and was highly correlated with the standard polysomnography scoring methods. These algorithms are developed in such a format that they can be implemented in real-time as well. That will open up the possibility of integrating these algorithms with the rapidly advancing ambulatory EEG monitors for novel applications such as ambulatory devices to predict onset of drowsiness and sleep.

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Measurement Of Frequency Response Of Pulse Oximeters

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Introduction: Overnight pulse oximetry is used to assess patients suspected of sleep apnea from the variability of arterial oxygen saturation. The identification of hypopneas during overnight polysomnography requires the measurement of transient changes of arterial oxygen saturation, therefore care has to be taken in assessing the frequency response of pulse oximeters. Often manufacturers do not report details of the dynamic response of these instruments. This information is crucial in order to evaluate the extent of desaturation events. For example, a 2% dip in oxygen saturation may represent a 4% decrease if only 50% of the amplitude is recorded due to an impaired frequency response of the pulse oximeter even if the instrument is calibrated accurately. The purpose of this study was to develop a simple laboratory method of measuring the frequency response of pulse oximeters.
Methods: We used a commercially available pulse oximeter simulator (SpO2 simulator Index 2, Bio-tek, Inc., Winooski, VT) to generate a step change in oxygen saturation and digitized the response recorded by the oximeter at 100Hz. We used a step increase of 10% for about 30 sec followed by a return to initial values. The instant that the step changes occurred was measured by closed tubing coupled to a pressure transducer overlying the switch used to induce the step change. The input signal was assumed to be a square wave and generated according to the timing of the pressure signal which was recorded simultaneously. For the portable oximeters that store data in a microchip, the input signal could not be accurately synchronized with the output signal. Instead, the timing of the input signal was approximated to the output signal and the phase relation was ignored. We used the maximum entropy method to estimate the frequency spectrum of the oximeter with commercially available software (Splus 6.0, Insightful Corp, Seattle, WA).
Results: Of the oximeters that we examined, the frequency responses that we measured were consistent with the use of moving average filters 3, 6 or 12 seconds in length and a dead time of similar magnitude before the output data is made available to the recording device.
Conclusion: This simple method for measuring the frequency response of pulse oximeters has some limitations particularly with portable pulse oximeters for which the phase shift cannot be determined. We recommend that manufacturers modify their instrumentation so that the frequency response of pulse oximeters can be measured and verified, as are other components of overnight polysomnography.

This research was supported by the loan of the pulse oximeter simulator from Bio-Tek.

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Night-To-Night Variability Of Periodic Limb Movements In Study Subjects With RLS, And How Might It Effect The The Design Of Pharmacotherapeutic Trials

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Introduction: Although patients with RLS often demonstrate an eleva-

tion in the periodic limb movement index (PLMI) during polysomnographic study, its clinical relevance is a subject of some debate for a variety of reasons: 1. In many patients, the PLMI varies widely from night to night. Drawing clinical conclusions on the basis of any given nights PLMI may not be valid. 2. Well-designed clinical trials have provided evidence of efficacy in RLS without necessarily demonstrating an effect on periodic limb movements. 3. Other objective PSG variables such as arousals, or total sleep time have at times shown little or no improvement despite signifigant reductions in the PLMI. 4. Subjective rating scales correlate poorly with the PLMI. Because the PSG represents the single most costly component of trials investigating new RLS therapies, and because the PLMI may not represent the most clinically relevant parameter, we questioned whether the design of a trial intended to demonstrate efficacy should be approached in a manner that would emphasize the assessment of polysomnographic variables such as the PLMI. Nobody has systematically sought to determine the minimum number of PSG determinations required to adequately asess anti-RLS therapy from the perspective the PLMI. Most recent trials have employed multiple polysomnographic nights (as many as six), but the required number of study nights for any given sample size might very well have been less. For instance, a recent open label trial found a statistically significant effect of GBN on the PLMI after just two baseline nights followed by a single treatment night (n=8 at p=.050)

Methods: Considering the potential sizeable financial impact of obtaining the same conclusion with less studies, we were interested in establishing by some means what might be the minimal design requirement from the standpoint of PSG evaluations. We used data derived from a Phase II open label pilot trial investigating the efficacy of an investigational drug in patients with at least moderately severe RLS. We enrolled patients with idiopathic RLS judged to be of at least moderate seveity by means of subjective (IRLS Rating Scale) and objective (PSG parameters). Patients were untreated or had there RLS medications withdrawn at least 7 days prior to baseline testing. The results of repeated PSG determinations of the PLMI in these patients over consecutive study nights will serve as the basis for the development of a Monte Carlo simulation study which will be used to investigate the problem using data models derived from the observations (including the measurement to measurement correlation structure). An analysis of the same design with randomly assigned treatment and control groups will also me made.

Results: The study sample was comprised of 10 patients. Two patients completed 3 consecutive pre-treatment nights, six patients completed four nights, and two completed five nights. The PLMI varied more from night-to-night within any given patient than it did from patient-to-patient within any given night. Standard deviations ranged from 3.6 to 33.2 between nights, and from 8.5 to 29.1 between patients. The mean PLMI +\-SD for patients was 28 +/-19.8, and for study nights was 28 +/-14.2.

Conclusion: 1. Large night-to-night variability was identified in a sample of drug-naive subjects undergoing repeated PSG measurements on consecutive nights in the context of a clinical trial. 2. Although preliminary, an approach whereby statistical modeling is used to determine a-priori, the number of measurements required is not only possible, but relevant to the cost-effective use of PSG in the design of future studies.

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Physiological State May Confound Seizure Prediction Algorithms Using Nonlinear Metrics

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Introduction: Analysis of all-night sleep studies of 7 young patients (ages 4 to 17) with normal polysomnograms reveal a strong dependence of nonlinear EEG measures on physiological state and sleep stage.

Methods: Maximum likelihood correlation dimension and Kolmogorov entropy values were calculated for consecutive 30-second epochs of EEG recorded from locations C3, O2, T3, T6, Fz and Cz at a sampling rate of 200 Hz. Standard Rechtschaffen and Kales scoring was used to label each epoch for physiological state (i.e. wake, REM, and sleep stages 1 through 4). The means of these metrics for each state were calculated for each patient and each electrode.

Results: A 6-state X 6-electrode two-way repeated measures analysis of variance on these mean values showed a significant effect for state on correlation dimension (p=0.001) and for electrode location (p=0.039), state (p=0.012) and electrode-state interaction (p=0.019) on Kolmogorov entropy. Absolute differences between the values of the nonlinear metrics for stage 4 sleep and mean waking values were comparable to changes reported to anticipate epileptic seizures in earlier studies. The median difference in correlation dimension was 1.12, while the median change in Kolmogorov entropy was 7.03 bits/second. Much larger changes were common, with more than 25% of stage 4 epochs showing a difference from wake of at least 2.01 in dimension and 12.28 bits/second in entropy.

Conclusion: These results suggest that automated algorithms which attempt to provide warnings of impending seizures based on amplitude changes in nonlinear EEG metrics must account for physiological state as a confounding factor.

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Independent Components Analysis of Sleep Evoked Potentials

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Introduction: The nonREM sleep averaged evoked response reliably shows a series of components, although debate exists as to the extent to which each relates to the presence of K-complexes in the average. This study uses independent components analysis (ICA) to investigate the impact of K-complexes on the underlying generator structure of nonREM sleep ERPs.

Methods: Data were collected from 10 young subjects (4 males) aged from 21 - 29 yrs (mean = 24.2), using Fz, Fcz, Cz, Cpz, Pz, and O2 EEG sites filtered with a bandpass of 0.3-30 Hz. Auditory stimuli (1000 Hz, 50 ms duration tones) were presented binaurally at 80 dB using insert earphones, with a random ISI between 15 and 30 seconds during stage 2 sleep. Responses were averaged separately depending on whether a K-complex was (KC) or was not (KC-) present in the response. For each data set a total of 6 ICA components were generated using Scan 4.3.1 software (Compumedics-Neuroscan, El Paso, Tx). ICA components were only regarded as signals if the signal to noise ratio (SNR) was greater than 1. The ICA components were auto scaled and then peak latency and amplitude values are determined for each component. Mean ± standard deviations are presented. The P2 and N350 component amplitudes and SNR values for each condition were compared using Wilcoxon signed rank tests.μ

Results: In the KC averages, all 10 subjects produced an N550 related component, with a mean amplitude of 87.7 (± 29) μV and a mean SNR of 27.9 (± 19.7). This component was present in 6 of the 10 KC- averages with a reduced mean amplitude of 14.2 (± 8.6) μV and an SNR of 2.49 (± 1.1). All 10 subjects produced an N350 component in the KC averages with a mean amplitude of 42.3 (± 21.4) μV and a mean SNR of

10.7 (± 9.5). This component was present in 8 of the 10 KC- averages, with a reduced amplitude of 14.1 (± 9.7) ($p < .05$) μV and a reduced SNR of 2.1 (±1.5) ($p < .05$). 8 of the 10 subjects produced a P2 component in the KC averages, mean amplitude of 10.5 (± 10.2) μV and SNR of 4.6 (±3.4) and it was also apparent in 8 of the 10 KC- averages, mean amplitude 9.5 (± 3.8) μV and SNR of 1.5 (±0.6). All 10 subjects produced a P900 component in the KC averages, mean amplitude 28.4 (±17.9) μV, mean SNR 10.3 (± 9.58). This was present in only 1 subject in the KC- average. An additional component at around 510 msec was present in the KC- averages of 5 subjects, mean amplitude of 12.1 (± 5.0) μV, mean SNR 1.6 (± 0.6).
Conclusion: The data indicate that the P2 is unaffected by K-complex presence or absence. The N550 and N350 generators are, however, still active although much reduced in most subjects in KC- averages. In 9 out of 10 subjects P900 was exclusively linked to K-complex presence. The additional component present in some subjects' KC- averages appeared to relate to the positive end of a vertex sharp wave. The data highlight the utility of ICA as an analytic tool to investigate sleep EEG responses.

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Electronic Diaries Improve Precision of Self-Reported Sleep Data: A Randomized Comparison to Paper Diaries

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Introduction: Paper sleep diaries are the primary method of collecting self-report subjective data in clinical trials. However, Personal Electronic Diaries (PED) have inherent advantages compared to paper diaries in terms of improving compliance, reducing recall bias, and insuring data quality. This study reports results of a randomized comparison of electronic diaries and paper diaries which demonstrate that an electronic diary improves the precision of self-reported sleep data. This increased precision could translate into the ability to conduct smaller studies with the same statistical power.
Methods: Patients aged 30-75 with chronic primary insomnia were randomized to a PED Study Arm (n=36; PED from PHT Inc., Boston, MA) or Paper Study Arm (n=32). There was a one-week washout period followed by 4 weeks of usual care with an FDA-approved hypnotic. Each day patients completed a Morning Questionnaire and Evening Questionnaire. A one-week recall version of the Pittsburgh Sleep Quality Index was also completed during clinic visits at screening, baseline, and Week 4. Efficacy of treatment was assessed by analysis of change from baseline (end-of-washout) to Week 4 of treatment.
Results: For self-reported total sleep time, the PED and Paper Arms yielded nearly identical estimates of change from baseline to Week 4 (i.e., Paper=118min (SD=91) vs PED=109min (SD=58)) but the precision of the PED arm was 36% better than the Paper Arm (1-58/91=.36). For self-reported sleep latency, the PED Arm detected a larger treatment improvement than the Paper Arm (i.e., Paper=-66min (Coeff. Var.=149) vs PED=-94min (Coeff. Var.=120)) and also had 20% improvement in precision (1-120/149=.20). The distributions of the data from the Paper Arm exhibited noticeable peaks of data which appeared to represent digit preference probably due to recall bias. The distribution of PED data did not exhibit any signs of digit preference. Precision also improved approximately 25% for two 4-level Likert scales in the sleep diary—sleep quality and ability to concentrate. The automatic time and date stamp on PED entries proved that patients completed over 92% of their entries in compliance with the protocol time windows. Paper diary patients completed 96% of their assessments but it could not be verified how many entries were made late (e.g., "parking lot compliance").
Conclusion: These results represent the first randomized head-to-head comparison of the precision and accuracy of self-reported sleep data from personal electronic diaries versus paper diaries. In these patients, the PED technology improved the precision of the sleep measures and appeared to reduce recall bias. These findings suggest that an insomnia clinical trial with primary endpoints based on self-report sleep diaries could be conducted with fewer patients while maintaining similar statistical power because of the increased precision of personal electronic diaries.

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A Multitrait-MultiMethod Analysis of Sleep Log and Actigraphy Assessment in Adolescents Recovering from Substance Abuse

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Introduction: Many clinical and research settings now utilize actigraphy as an objective supplement to daily sleep logs in the assessment of sleep and wake patterns because of cost-effectiveness and feasibility advantages over polysomnography. However, there is some question as to whether these instruments can consistently measure commonly reported sleep parameters. The data that have been reported comparing these two assessment methods indicate discrepancies between most if not all sleep variables, particularly in populations with disturbed sleep. This report examines the relationship between baseline sleep log data and wrist actigraphy on a range of sleep variables for adolescents who have been in treatment for substance abuse using a multitrait- multimethod (MTMM) approach.
Methods: The 33 participants (19 males and 15 females) ranged in age from 14-18 years old and described themselves as having persistent trouble falling asleep, staying asleep or experiencing daytime sleepiness. Participants were asked to complete an 11-item sleep log every morning and wear a wrist actiwatch every night for a minimum of seven consecutive days. Actigraphy sleep measures were obtained using the default settings of the Mini Mitter Co. Inc. software package (Version 3.3). Analyses only included data from days when both sleep diary and actiwatch were available. The sleep variables used in this study were sleep onset latency (SOL), # of awakenings (#awake), wake after sleep onset (WASO), time in bed (TIB), total sleep time (TST), and sleep efficiency (SE).
Results: MTMM analyses normally involve reporting correlations at the variable level but to simplify the results we computed four unit-weighted factors. A MTMM matrix was used where actigraphy (A.) and sleep logs (D.) were tested as method factors and sleep (S.) and wake (W.) were tested as trait factors. The sleep variables of TIB, TST and SE were loaded on the S-trait factor and SOL, #awake, WASO, TIB and SE were loaded on the W-trait factor. There was a low correlation between sleep logs and actigraphy ($r = .20$). Monomethod-heterotrait correlational values (A.S. vs. A.W. = .70, D.S. vs. D.W. = .72) were greater than heteromethod-monotrait values (A.W. vs. D.W. = .20, A.S. vs. D.S. = .12). The six individual sleep variables correlated well with each of the four computed factors. For the actigraphy factor and sleep log factor at least five of the six sleep variables had a factor-loading correlation above .40.
Conclusion: Measurement ideally results in trait estimates, untainted by method or method-by-trait variance. Unexpectedly, our results indicate the presence of relatively strong methods factors. However, when the methods of actigraphy and sleep logs are used simultaneously, our results indicate that they may provide unique variance or different estimates of the trait factors. This variance may be the result of differing

sensitivities of the instruments or other unidentifiable influences. Still, the use of these instruments appears to be warranted in clinical and research settings when used simultaneously but further investigation of these methods is needed. Compliance with assessment procedures remains a major issue with this population and caution in interpreting the generality of the results is warranted.

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Novel, Quick-Duration Test of Sleepiness Based on Combined EEG and Reaction Time (Auditory) Analysis

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Introduction: An easy-to-administer, quantitative and quick-duration method of measuring sleepiness is greatly needed for sleep research and will have tremendous clinical utility in sleep medicine. In fact the new National Sleep Disorders Research Plan explicitly recommends development of quantifiable, non-invasive, and relatively rapid methods of assessing sleepiness. This need arises partly because the current clinical objective tests of sleepiness, mean sleep latency test (MSLT) and maintenance of wakefulness test (MWT), though scientifically validated and well standardized, are time-consuming and are limited to the specialized sleep laboratory requiring elaborate physical infrastructure and human resources. Combining an ambulatory wireless EEG monitor with an auditory-based continuous performance test, a novel quick-duration (15 minute) test of sleepiness has been developed and tested in subjects with adequate sleep as well as in sleep restricted individuals.
Methods: Six normal volunteers with adequate prior night sleep and six normal sleep-restricted volunteers (prior night sleep was at least 3 hours less than their normal sleep duration) participated in this study. The test duration was 15 minutes and the protocol consisted of instructing the subjects who were resting in bed with their eyes closed to respond to a target auditory tone (and ignore the non-target tone) by pressing a push-button while their EEG was being acquired. From the EEG and the reaction times, several indices relating to drowsiness and performance were computed and compared between the two groups of subjects. The Drowsiness Index was derived by performing spectral analysis on EEG and characterizing the relative distribution of power in the alpha and sub-alpha bands. Higher values of this index are indicative of less alpha and more sub-alpha power (which is usually associated with increased drowsiness and sleep onset). The Reaction-Time Index was based on the number of times that the subject response was longer than 500 milliseconds. Data analysis was performed after 3 minutes into the test (to allow acclimation) and had a duration of 180 seconds.
Results: The Drowsiness Index was significantly ($p < .05$) larger in sleep deprived subjects (mean=1.17, range: 0.29-3.7) compared to subjects with adequate sleep (mean=0.16, range: 0.09-0.22). Subjects with adequate sleep had a significantly smaller ($p< .047$) reaction-Time Index (mean=1, range: 0-2) compared to sleep restricted subjects (mean= 57.5; range: 2-156). Finally, the pooled data from the two groups showed a correlation coefficient of 97% between the EEG-based Drowsiness Index and the Reaction-Time Index.
Conclusion: This new quick-duration test of sleepiness performed very well in differentiating subjects who were intentionally sleep restricted compared with those with adequate sleep requiring only the first six minutes of the available data. Currently, this test is being utilized in a multi-center clinical evaluation of patients with excessive daytime sleepiness. The performance of this test will be compared against the gold-standard MSLT/MWT tests.

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Comparison of a New Nasal Snoring Sensor to a Conventional Neck Snore Sensor

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Introduction: Traditional snore sensing has been accomplished with a piezo-ceramic transducer placed on the neck. In some patients with large necks, this may prove challenging to the detection of snore events. A device has been recently introduced that may provide more sensitive snore detection during polysomnograhy. The device utilizes polyvinylidene fluoride film (PVDF) to create a sensor that is fit over the nose. The sensor is designed to adhere to the fleshy portion of the nose. It has been observed that this area vibrates significantly regardless of where in the throat or nose the snore is generated. The purpose of this study was to compare the differences in snore event identification between the nasal and neck sensors.
Methods: 19 patients scheduled for routine split-night polysomnographic testing for sleep-disordered breathing were evaluated with both nasal and conventional ceramic snoring sensor placed on the neck. Sampling was performed during both baseline acquisition and NCPAP titration. Filter settings: < 10 Hz to > 120 Hz, sampling rate > 200 samples/sec. Each patient had the nasal sensor applied first (Over The Nose Sensor - Dymedix Corporation, Minneapolis, MN), with the placement being over the patient's nose, below the bridge. The neck sensor was applied second, placed on the patient's neck 1-2 inches lateral from the midline. Signals were recorded simultaneously, resulting in two separate snore channels. Following data acquisition, both signals were analyzed using an automated snore analysis algorithm provided by the Compumedics Profusion PSG Analysis program, identifying events by signal strength threshold criteria. Analysis report values were: Total Snore Events, Snore Event Index.
Results: Mean (Standard Deviation) Total Snore Events: Nasal 362.5 (398.9) Neck 71.6 (40.4) $p<.01$; Snore Event Index: Nasal - 61.0 (64.3) Neck 12.2 (6.4) $P<.01$. In 13 of the 19 patients, the nasal sensor resulted in more events than the neck. Visual analysis of the PSG data revealed frequent snoring events which were recorded much earlier in the event with the nasal sensor as compared to the neck placed probe. Also, many snore events were recorded with the nasal sensor, but were not present with the neck placed sensor data.
Conclusion: The nasal sensor detected more snoring events than the conventional neck placed snore sensor. The difference may be related to the sensitivity of the PVDF sensor material or the sensor placement. Nasal placement may reduce the incidence of carotid pulse artifact, which could account for the 6 patients which recorded more events with the neck sensor. Nasal placement may allow increased snore signal strength in obese patients with large necks. These findings suggest that the use of the nasal snore sensor may be advantageous to the clinician as a sensitive method of detecting and displaying subtle, mild snoring events associated with upper airway resistance syndrome, as well as snoring events associated with more frank upper airway obstruction in patients with large necks in which the snoring signal is diminished.

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Polysomnogram Interpretation: A Comparison of Trained Versus Untrained Physicians

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Introduction: Polysomnography (PSG) interpretation is commonly performed by physicians lacking formal training in Sleep Medicine. It is unclear whether PSG interpretation is better performed by trained physicians in Sleep Medicine. This study seeks to determine whether a trained sleep medicine board certified physician performs better interpretation of PSG than formally untrained counterparts.
Methods: Adult subjects aged 18 and above presenting for PSG were eligible for the study. All subjects underwent informed consent prior to enrollment. All PSG data was collected in a blinded prospective fashion. Initial PSG with scoring and interpretation by untrained Sleep Medicine physicians was performed at Landstuhl Army Regional Medical Center in Germany with subsequent blinded scoring with interpretation by a trained sleep medicine board certified physician at Walter Reed Army Medical Center in Washington DC.
Results: Pearson's Correlation Periodic limb movements between sites: 0.854 (N=49) Apnea hypopnea index between sites: 0.495 (N=49) Diagnostic agreement between sites: 0.526 (N=46)
Conclusion: This study shows poor correlation of apnea/hypopnea index and diagnosis between physicians Sleep Medicine board certified and trained versus physicians untrained in Sleep Medicine. The study indicates that a trained physician frequently came to different conclusions with the same PSG data versus untrained physicians. Further research in assessing agreement between trained physicians PSG interpretations is needed to better assess the impact of training and Sleep Medicine board certification on PSG interpretation.

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SLEEP Model Assessment of Injury Risks

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Introduction: Drowsy driving is a serious safety issue on highways. A sleep management education tool, SLEEP Model, has been developed to educate people on the consequences of poor sleep management, including injury risks.
Methods: SLEEP Model predicts performance efficiencies associated with sleep input, time of day, use of caffeine, and use of alcohol. Increased injury risk is related directly to loss in performance, which can be caused by either alcohol or insufficient sleep or both. The predicted performance from SLEEP Model for passive behavior associated with 0.05 blood alcohol is approximately that for 18 to 20 hours of sleep debt, similar to results reported by Lamond and Dawson (1999). Injury risk data associated with alcohol use were obtained from Dr. Daniel Vinson at the University of Missouri Medical Center. After calibration, SLEEP Model predicted the increase in injury risk with alcohol use (R2 of 0.85, statistically significant at the 0.05 probability level). The upper and lower 95 percent confidence values were predicted (R2 values of 0.98 and 0.76 respectively) by varying the rate of drinking between maximum and minimum extremes. Significant levels were 0.001 and 0.05 respectively. Once the injury risk component was calibrated for performance changes associated with alcohol, it was available to predict injury risk associated with sleep management.
Results: SLEEP Model predicts the increase in injury risks for a specified period of time. Individuals can assess their increase in potential for injury risk at work, for driving, or for some other activity. SLEEP Model does not predict the absolute risk of injury; instead, it predicts the increase in injury risk. For example, Sivak and Flannagan (2003) reported that the risk of being in a fatal car accident associated with traveling about 700 miles is 5.09 x 10-6. An injury risk increase 10 times normal would produce a final risk of a fatal injury of 5.09 x 10-5. The predicted increase in injury risk for a young adult (age 28) for averages of 8, 6, and 4 hours of sleep over a three-week period were 0, 18, and 30 times normal respectively. Driving during the same period of time after one night of no sleep increases injury risk 16 times normal, about the same as a steady-state, 6-hour daily sleep amount.
Conclusion: Based on simulations with SLEEP Model for typical sleep amounts often reported for adults, many people are driving with at least an order of magnitude increase in risk of accident. The results from SLEEP Model can be used to educate people on the dangers of driving after poor sleep management and how their injury risk can be changed with caffeine or sleep. Injury risks also greatly increase when people try to work/drive during periods normally used for sleep.

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The Negative Impact of Sleep Disorders on Students' Behaviors and Academic Performance

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Introduction: While doing a national validation study of the Sleep Disorders Inventory for Students (SDIS), academic and behavioral information was collected on 595 students to determine if a relationship exists between sleep problems and academic or behavioral performance. Students ranged in age from 2-to-18 years of age and represented most educational classifications, and there was a broad representation of students with Mental Health (DSM-IV) diagnoses.
Methods: A correlation analysis was conducted on 453 students from 6-through-18 years of age to determine the relationship between Grade Point Average (GPA) and amount of sleep problems (measured by the SDIS). A second correlation analysis was completed on the total sample (595 students) to measure the relationship between sleep problems and a summation of 12 behaviors rated by parents on a 7-point Likert scale (irritable, moody, distractible, impulsive, depressed, aggressive, high activity level, oppositional/defiant, shy, withdrawn, frustrated, and tantrums). ANOVAS were conducted to determine differences in the amount of sleep problems (1) between educational classifications, and (2) between students with DSM-IV diagnoses versus no diagnosis. Retrospective studies using paired t-tests were undertaken on 28 students to determine whether correction of the sleep disorder resulted in GPA or behavioral improvements 6 months-to-2 years post-treatment.
Results: There were negative correlations between GPA and severity of sleep problems: Reading = -.32 ($p<.0001$); Math = -.33 ($p<.0001$); Writing = -.32 ($p<.0001$). Students with many sleep problems had lower GPAs and student with few sleep problems had higher GPAs. As sleep problems increased with age, GPA dropped. Positive correlations existed between the Total Sleep Problems Index and the Total Behavior Problems score for all ages combined (.57, $p<.0001$). As sleep problems increased in severity with age, behavior problems also increased (3-5 yrs., .42, $p<.0001$; 6-10 yrs., .59, $p<.0001$; 11-14 yrs., .65, $p<.0001$; 15-18 yrs., .63, $p<.0001$). Students with few sleep problems had few behavior problems. Anovas using Tukey analyses comparing differences in sleep problems across educational classifications resulted in significantly higher sleep problem scores for special education students (EH, OHI,

DD, SLI, MR, SLD) than Gifted students (p<.05). The same was true for most special education classifications compared to General Education. Further Anovas using Tukey analyses indicated that students diagnosed with Depression, Oppositional Defiant Disorder, ADHD, or Asthma had significantly higher scores on the Total Sleep Problems Index than students with no DSM-IV diagnosis (p<.05). Results of paired t-tests demonstrated that GPA improved in all academic areas post-treatment of the sleep disorder (Reading = .29, t-value = 2.60, p = .016; Math = .25, t-value = 2.77, p = .01; Writing = .38, t-value = 2.84, p = .009). Total Behavior Problem scores decreased post-treatment (t-value=6.17, p<.0001), and 10 out of 12 individual behavior problems decreased: oppositional/defiant (t-value=5.48, p<.0001), frustrated (t-value=5.67, p<.0001), irritable (t-value=5.23, p<.0001), distractible (t-value=4.46, p<.0001), moody (t-value=4.15, p<.0003), aggressive (t-value=3.97, p=.0005), depressed (t-value=3.86, p=0006), withdrawn (t-value=3.64, p=.0011), tantrums (t-value=3.47, p=.0017), and impulsive (t-value=3.42, p=.002).

Conclusion: These results indicate that sleep disorders have a significant impact on academic and behavioral functioning of students, and that early correction of these sleep disorders could result in significant improvements in academic and behavioral performance. It is crucial that educators and psychologists are informed about this educational information so that they will screen and refer students with possible sleep disorders to sleep specialists for treatment before making special education or mental health diagnoses.

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Lack of Exposure to Sleep Knowledge Prior to College: A Possible Cause of Poor Sleep Habits

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Introduction: At present, the American population continues to ignore the importance of sleep. High school students are an important subgroup because they typically have academic and extracurricular schedules that engender severe sleep loss while at the same time they are usually acquiring new skills that are especially vulnerable to sleep deprivation, such as learning to drive. As an approach to assessing recent high school curricula, Stanford University undergraduates, particularly freshmen, are being surveyed about their prior exposure, if any, to sleep education.

Methods: Questionnaires are being administered to small groups of Stanford University undergraduates in the dormitories at 6 PM prior to an hour-long talk by one of the investigators (WCD). The survey asks about any systematic sleep education prior to college, as well as assesses sleep habits and beliefs about sleep. The average group size has been 32 students. To date, 191 questionnaires have been completed. This activity will continue throughout the academic year with an eventual target of the entire freshman class (approximately 1650 students).

Results: Preliminary data reveal that the Stanford freshmen population originates from diverse ethnic, socioeconomic, and geographic backgrounds from across the United States. Ninety percent (90.05%) of those sampled to date had received no exposure whatsoever to sleep knowledge prior to college. The other ten percent had received only minimal systematic teaching about sleep. The survey also revealed that undergraduates generally have poor sleeping habits. On school nights, 45.03% of the students sampled only sleep 5-6 hours, 42.41% only sleep 7-8 hours, 2.7% only sleep 3-4 hours, and only 9.95% even sleep 8-9 hours/school night. None of the students sampled averaged more than 9 hours per night. Furthermore, on non-school nights, sleep deprivation continues as the largest portion of students, 45.26%, still only obtains 8-9 hours of sleep followed by 28.42% who sleep 7-8 hours, and 7.89% who sleep 5-6 hours. Only 17.89% sleep 10 or more hours. As a likely consequence of the above, 30.89% of all students feel sleepy all the time, while a majority of students feel sleepy frequently throughout the day. As an example, at the time of the survey, 43.98% of students indicated they felt sleepy at that moment.

Conclusion: From 1990-1992, the National Commission on Sleep Disorders Research was mandated by the United States Congress to study the impact of sleep deprivation and sleep disorders in American society. It found that high school students and college undergraduates were largely unaware of issues involving basic knowledge about sleep. Current freshmen undergraduates are less than a year removed from high school. To the extent that Stanford undergraduates have received an excellent high school education but were not exposed to sleep knowledge, we may conclude that ten years after the Commission's report and recommendations to the Congress, sleep education continues to be absent from all or nearly all high school curricula. This lack of sleep education is highly likely to be a factor in the demonstrated poor sleep habits of college undergraduates.

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Treatment Choices for Obstructive Sleep Apnea among Non-Sleep Specialist Physicians

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Introduction: Physicians in practice frequently encounter patients with sleep apnea. Obstructive sleep apnea occurs in 4% of men and 2% of women age 30-60. Sleep apnea is associated with increased risk of hypertension, cardiovascular disease and stroke. CPAP is generally considered to be the most effective treatment of obstructive sleep apnea, although alternative treatments are effective in selected cases. In this study of non-sleep specialist physicians (NSSPs), the choices of most appropriate treatment for mild, moderate and severe sleep apnea were analyzed.

Methods: 770 NSSPs were identified by databases of active staff of a teaching hospital and faculty of University of Illinois College of Medicine at Peoria. Subjects responded anonymously to a survey sent by U.S. mail. Questions were objective (multiple choice) except those regarding demographic data.

Results: A total of 139 responses (18.1%) were received. Subjects were asked to choose the single most appropriate treatment option for mild, moderate, and severe obstructive sleep apnea with associated excessive daytime sleepiness. The responses of primary care physicians (PCPs) and specialists (listed as PCP / specialist for mild, moderate, and severe apnea respectively) were as follows: Weight loss 35 (49.3%) / 20 (47.6%), 4 (5.7%) / 2 (4.8%), 0 / 1 (2.4%); CPAP 8 (11.3%) / 6 (14.3%), 49 (70%) / 22 (52.4%), 39 (57.4%) / 15 (36.6%); Mandibular advancement device 1 (1.4%) / 0, 2 (2.9%) / 1 (2.4%), 0 / 1 (2.4%); Maxillomandibular advancement surgery 0 / 0, 0 / 1 (2.4%), 1 (1.5%) / 0; Uvulopalatopharyngoplasty 1 (1.4%) / 1 (2.4%), 2 (2.9%) / 3 (7.1%), 2 (2.9%) / 3 (7.3%); Laser Assisted UvuloPalatectomy 0 / 1 (2.4%), 1 (1.4%) / 0, 4 (5.9%) / 1 (2.4%); Positional Therapy 19 (26.8%) / 1 (2.4%), 4 (5.7%) / 0, 5 (7.4%) / 1 (2.4%); Not Sure 7 (9.9%) / 13 (31.0%), 7 (10%) / 14 (33.3%), 17 (25%) / 19 (46.3%). There was a significant difference between PCPs and specialists for treatment of mild sleep apnea (Pearson Chi-Square=18.128, p=0.006). There was no significant difference between PCPs and specialists for moderate and severe sleep apnea treatment.

Conclusion: While there is no single best treatment for all cases of obstructive sleep apnea, CPAP is generally considered the most effective treatment for most. Interestingly, both groups of physicians chose CPAP (PCPs 96 [46%], SPs 43 [34.4%]) less than half the time for all cases

combined. The Not Sure choice was selected by a relatively small number of PCPs (31 or 15%), and by significantly more specialists (19 or 36.8%). This study demonstrates continued opportunity for increased knowledge among NSSPs regarding most effective treatment for mild, moderate and severe obstructive sleep apnea. PCPs and specialists may need different types of sleep-related continuing medical education.

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Sleep Learning and Education Evaluation for Psychiatry: a SLEEP study

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Introduction: Sleep disorders are common, yet often unrecognized in many clinical settings. However, several researchers have noted deficiencies of sleep education in medical students and primary care physicians. Many of these patients may present to a psychiatrist, yet only two studies assess sleep disorders education for psychiatrists. The aim of this study is to assess the knowledge of sleep medicine in psychiatry residents with Zozula's validated Assessment of Sleep Knowledge in Medical Education (ASKME) survey.
Methods: Psychiatry residents at one training program completed the 10-minute ASKME survey in the summer of 2002 and 2003, without receiving answers at either time. IRB approval was obtained and all residents approached voluntarily participated and were informed that the results would not affect their evaluations or training. 22/29 (76%) of residents, divided approximately equally between 4 years of training, completed the survey in 2002, prior to any lectures in sleep medicine. The survey was then re-administered to residents in the summer of 2003, by which time training had included a one-hour lecture in sleep disorders, and a one and a half-hour videotaped conference on sleep physiology. 24/31 (77%) residents completed the ASKME survey in 2003 and these results were then compared to the previous year.
Results: One way Analysis of Variance (ANOVA) was used to assess whether differences in resident scores reached statistical significance. Overall, while residents' improved with each year of training, this did not reach statistical significance in either the 2002 group (between all 4 classes of residents, p=0.18) or the 2003 group (between all 4 classes of residents, p=0.70). Scores from the junior residents in 2002 (PGY I = 58.7%, PGY II = 56.3%) were comparable to medical students from Zozula's initial survey (Medical students = 56.3%), while corresponding scores from PGY III (67.3%) and IV (79.3%) residents were comparable or superior to primary care physicians (66.3%) from her study. The ASKME survey also covered several areas of sleep knowledge. The Wilcoxon Rank Sum Test was used to assess whether changes in scores from the 2002 results in different areas of sleep knowledge were statistically significantly different from results obtained in 2003. Residents showed the most improvements in circadian sleep wake principles (+20.3%, p=0.09), effects of drugs/alcohol on sleep (+11.3%, p = 0.17) and sleep architecture (+9.9 %, p= 0.27). However, narcolepsy (-16.9%, p= 0.17) showed a drop in scores.
Conclusion: As psychiatry residents advance through training, sleep knowledge improves. Several factors may play a role in this improvement, including the didactic curriculum, and the clinical experiences of residents, particularly in their senior years. By the end of psychiatry residency training, residents' knowledge in sleep medicine may be comparable or superior to other practicing primary care physicians. Psychiatry residents may have more knowledge in circadian sleep/wake principles, effects of drugs/alcohol on sleep, and sleep architecture. Areas in the curriculum to focus on may include improving knowledge in narcolepsy, as many of these patients may initially be referred to psychiatrists prior to diagnosis and for ongoing management.

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Prior Education and Interest in Continuing Medical Education in Sleep Medicine among Practicing Physicians

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Introduction: Physicians in practice often encounter patients with sleep-related symptoms, but many lack education in sleep. Sleep disorders are very common, can have significant consequences, and most remain undiagnosed. Non-sleep specialist physicians in clinical practice (NSSPs) need to have a working knowledge of clinical sleep medicine. In order to design effective continuing medical education (CME) in sleep for NSSPs, recognition of prior sleep education, and an understanding of their interest in CME are important.
Methods: 770 NSSPs were identified by databases of active staff of a teaching hospital and faculty of University of Illinois College of Medicine at Peoria. Subjects responded anonymously to a survey sent by U.S. mail. Questions were objective (multiple choice) except those regarding demographic data.
Results: One hundred thirty-nine responses (18.1%) were received. Subjects were asked to estimate how many hours of education in normal sleep physiology and sleep disorders they received at each level of training. Primary care physicians (PCPs) reported significantly more hours of sleep disorders teaching in medical school (2.62 [SD 2.48]) and fellowship (1.19 [SD 2.28]) than specialists (1.47 [SD 2.13] in medical school) (0.21 [SD 0.57] in fellowship), (p= 0.011 and p= 0.033, respectively). There were no significant differences in reported hours of teaching of normal sleep physiology in medical school, or sleep disorders in residency or CME. Subjects reported a mean total of 9.54 hours of teaching in normal sleep physiology and sleep disorders throughout formal training and 4.36 (SD 5.98) hours in CME. Twenty-six (19%) of all subjects reported no education in sleep at any level. Thirty-eight (27%) had none in residency. Thirty-three subjects (26.6%) indicated they had had no sleep CME. Reasons for having no sleep CME included none available (58%), not interested (19%), and not enough time (13%). Types of CME in sleep medicine were ranked as most helpful and, separately, as those which subjects would be most likely to do. The following options were ranked (1=least, 8=most) as follows (most helpful, would most likely do): half day seminar (6.44, 5.28), 1 hour CME lecture (5.95, 6.89), sleep course at your national meeting (5.66, 3.91), written cases with CME credit (5.13, 5.35), written cases (4.39, 4.62), 1 hour case discussion (4.91, 5.66), nothing (3.22, 3.89), other (2.58, 2.71).
Conclusion: The findings that 19% of subjects had no sleep education at all and 27% had none in residency suggest many NSSPs are not sufficiently educated in sleep medicine. The difference in hours of sleep education in medical school and fellowship recalled by PCPs compared to specialists may reflect a difference in interest or knowledge in sleep. As sleep disorders are common and can have significant consequences, further education is necessary. Most subjects indicated they were interested in sleep CME, with a 1 hour CME lecture ranked as the type they would most likely do. This suggests the curriculum should be brief and specific. Further studies are needed to determine what type of CME would be most effective.

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Evidence Supporting the Need for Sleep Medicine Education in Pharmacists

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Introduction: Sleep disorders are highly prevalent, affecting nearly 70 million Americans. In a national survey, approximately 40% of adults reported disturbed sleep. The purpose of this study was to substantiate the need for sleep medicine education in pharmacists, one of the primary healthcare professionals on the frontline of patient care. Although the need for sleep medicine education has been assessed in other healthcare professionals, to our knowledge, it has not been assessed in pharmacists.
Methods: At a regional continuing education conference for pharmacists, 278 attendees were evaluated on their knowledge of sleep medicine. The participants were asked to take a pre-test before a seminar on factors that promote quality sleep, with a particular emphasis on understanding the hormone melatonin. The seminar was the final talk of the day, given at 4:00pm on Saturday. After the seminar, participants took a post-test to assess how much information they retained. Each individual was given a No. 2 pencil and a Scantron. Five questions, projected on the screen, were read aloud and the participants were asked to choose the best answer from the projected choices (A-E). After the presentation, the same questions were projected and read aloud. The participants were again asked to choose the best answer. However, this time, the answer choices were rearranged.
Results: On the pre-test, nearly 80% of the participants answered only two or fewer questions correctly. After the seminar, on the post-test, 77% of the participants answered three or more questions correctly. Even individuals having no correct responses on the pre-test significantly improved their knowledge of sleep medicine with 63% of these participants having two or three correct responses on the post-test. Furthermore, a comparison of correct responses between the pre-test and post-test reveals a significant increase in the percentage of correct responses on the post-test. In addition, the format of the questions allowed the examiners to differentiate between individuals who retained the maximal information and those who mastered the major points, but missed the minor ones.
Conclusion: This study compared the baseline knowledge of sleep medicine in pharmacists to the knowledge acquired through a continuing medical education seminar. The results of this study indicate that continuing medical education seminars are beneficial to pharmacists. In addition, this study provides evidence supporting the need for sleep medicine education in this group of healthcare professionals.

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Evaluation of the NASA Education and Training Module on Alertness Management: Knowledge Gained and Organizational Impact

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Introduction: Since 1993, the NASA Ames Research Center's Fatigue Countermeasures Group has conducted alertness management Education and Training Module (ETM) workshops to transfer scientific knowledge concerning fatigue and alertness management to the operational environment. Data collected (N=240) in a 1998 survey, conducted by Rosekind and colleaugues, demonstrated that the ETM had great impact with 58% of the respondents reporting organizational changes and receiving an average rating of 4.4 for usefulness on a 5-point scale. Data collection has begun for a follow-up study to examine: 1) the extent attendee's level of knowledge regarding fatigue and alertness management issues change after having participated in the ETM and 2) which aspects of an organization change after having attended the workshop.
Methods: Data were collected from 23 workshop attendees (mean age = 37.90 ±10.45 years) who participated in the workshop during a six-month time period. The workshop is a two-day, on-site workshop consisting of live presentations of information on sleep, circadian rhtyhms, fatigue, performance, fatigue countermeasures and scheduling techniques. Attendees completed a 17-item questionnaire to test their basic knowledge of the workshop topics prior to (pre-ETM) and upon completion of (post-ETM) the ETM to assess the knowledge gained. Additionally, an Attendee/Organizational Characteristic (AOC) questionnaire was administered to collect basic demographic information, and an organizational Alertness Management Safety Evaluation (AMSE) questionnaire was distributed that was developed to evaluate an organization's alertness management activities.
Results: All 23 attendees completed both the pre-ETM and post-ETM questionnaires. As seen in the AOC responses, 16 of the 23 participants (n=15 military; n=7 aviation; n=1 other) reported that they held a position that enabled them to influence policy change within their organization. Preliminary analyses indicated that there was a significant increase ($t(22)=-3.894$, $p=0.001$) in the total number of correct responses between the pre-ETM (M=12.74 ±1.54) and post-ETM (M=14.61 ±1.75) questionnaire. Specifically, individual item analyses revealed a significant change in the frequency of correct responses between the pre-ETM and post-ETM questionnaire in areas related to the timing of circadian rhythms, healthy-adult sleep-need, and sleep disorders (McNemar's $\chi 2$ test indicate p=0.031, 0.039, 0.002 respectively). Of the 11 participants who completed the AMSE, nine indicated that their organization had no written policies concerning sleep disorders and ten do not offer employees information regarding sleep disorders.
Conclusion: Preliminary results suggest that ETM attendee's level of knowledge regarding fatigue and alertness management significantly increased after participating in the workshop, especially marked in areas regarding circadian rhythms, healthy-adult sleep-need, and sleep disorders. In addition, there appears to be a lack within organizations regarding information and policies addressing sleep disorders, but attendance during the workshop suggests that organizations are making efforts to try and develop alertness management programs. Data collection will continue, and a six-month follow-up survey evaluating the organizational impact after attending the workshop will be conducted to determine if policy change has occurred.

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Sizing and Fitting of Interfaces for Positive Airway Pressure Therapy: Is there any Advantage Gained by Providing a Hospital Based Service Compared to a Remote Sizing and Fitting Service Carried out by Individual Patients?

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Introduction: In the United Kingdom positive airways pressure (PAP)

therapy is most commonly established by hospital based practitioners (HBP). Establishing therapy includes patient education, pressure settings, device education and interface selection, sizing and fitting. Management Of Sleep Therapy® (MOST) is a new service which provides sleep therapy for diagnosed Obstructive Sleep Apnoea (OSA) and supports clinicians by removing the routine management of individuals PAP therapy. To be effective in providing a national service remote set-up is required in the majority of cases. If clinicians are to have confidence in relinquishing HBP initialisation of PAP therapy it is essential that the remote service provided is at least equivalent to traditional hospital based services. Previous studies have shown that compliance and adherence to PAP therapy is often multi-faceted, however, correct interface sizing is a primary issue in non-compliant individuals.

Methods: Mask Leak variables from 50 PAP naïve subjects, with a confirmed diagnosis of OSA enrolled on MOST were recorded at day 7 using an Encore Pro® SmartCard™ on a Respironics® REMstar® PAP device. The OSA group was evenly split between hospital initiated set-up (HIS) and remote set-up (RS).

Results: The Average Maximum Leak (AML), Average 90% Leak (AL90), Average Leak (AL) (lpm) and Average Time in Large Leak Per Night (ATLLN) (sec) was compared between the 2 groups using Mann-Whitney (2-tailed). AML RS 112.2±37.8 HIS 121.7±24.5 p =0.32. AL90 RS 44.9±12.6 HIS 49.8±10.6 p =0.07 AL RS 34.6±10.2 HIS 38.0±8.0 p<0.05 ATLLN RS 307.4±604.9 HIS 487±859.9) p<0.05. The 90th pressure centile was similar for both groups RS 10.2±2.6 HIS 9.9±2.4 cmH2O p =0.94.

Conclusion: This study demonstrates that in this particular group of subjects remote sizing and fitting of individuals on the MOST programme is as good when comparing it with traditional hospital based set-up.

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Comfort Levels of Non-Sleep Specialist Physicians in Diagnosis and Treatment of Sleep Apnea and Insomnia

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Introduction: Physicians in clinical practice encounter patients with a wide variety of symptoms. With experience, clinicians develop different levels of comfort in dealing with various types of presenting complaints. Sleep complaints are very common and can have significant consequences, but many physicians lack formal training in sleep medicine. This study sought to assess levels of comfort among non-sleep specialist physicians (NSSPs) in diagnosing and treating two common sleep conditions (sleep apnea and insomnia).

Methods: 770 NSSPs were identified by databases of active staff of a teaching hospital and faculty of University of Illinois College of Medicine at Peoria. Subjects responded anonymously to a survey sent by U.S. mail. Questions were objective (multiple choice) except those regarding demographic data.

Results: NSSPs were asked: How comfortable are you in your clinical practice with each of the following? (rating scale 0= Very Uncomfortable, 4= Very Comfortable) Seventy-three primary care physicians (PCPs) and 48 specialists responded [listed as PCPs (standard deviation), specialists (standard deviation)] as follows: Diagnosing sleep apnea without a sleep test or the assistance of a sleep specialist [1.33 (1.41), 1.75 (1.04)] p-0.004; Diagnosing sleep apnea with a sleep test but without the assistance of a sleep specialist [2.0 (1.69), 2.48 (1.28)] p<0.0005; Treating sleep apnea in your clinical practice without the assistance of a sleep specialist [1.25 (1.49), 1.71 (1.09)] p<0.0005; Diagnosing insomnia in your clinical practice, without a sleep test or the assistance of a sleep specialist [1.75 (1.39), 2.66 (1.13)] p<0.0005, Diagnosing insomnia in your clinical practice, with a sleep test but without the assistance of a sleep specialist [1.88 (1.55), 2.49 (1.28)] p<0.0005; Treating insomnia in your clinical practice without the assistance of a sleep specialist [1.5 (1.41), 2.57 (1.2)] p<0.0005.

Conclusion: NSSPs were generally not very comfortable diagnosing or treating apnea or insomnia without the assistance of a sleep specialist, although specialists were significantly more comfortable in each case than PCPs. This overall lack of comfort is not surprising, considering many NSSPs have little or no education in sleep medicine. It does, however, suggest many patients with sleep disorders may either remain untreated (which is a known problem), or may require a consultation with a sleep specialist for diagnosis and treatment. Since sleep disorders can have significant consequences, underdiagnosis is concerning. As sleep disorders are very common, consultation by a sleep specialist in every case would not be practical. Optimally, NSSPs would to be able to diagnose and treat many cases of apnea and insomnia, with sleep testing when clinically appropriate, and require specialty consultation for only the more difficult cases. Increasing comfort levels of NSSPs may be necessary for this to occur. Carefully designed continuing medical education in sleep medicine may facilitate this.

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Comparison of Sleep Homeostasis in BMAL1 KO Mice and Drosophila cyc01 and cyc02 Mutants

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Introduction: Recent data indicate that components of the circadian clock may also play a role in regulating sleep. Thus, mice with disruptions in genes such as Dpb, Clock, Npas2 and the cryptochromes exhibit modifications in several sleep parameters. Interestingly, both CLOCK and NPAS2 form heterodimers with BMAL1 allowing them to activate the transcription of downstream genes, some of which are known to be involved in sleep regulation. This relationship suggests that BMAL1 may also play a role a non-circadian role in sleep regulation Indeed, flies mutant for cycle (cyc01), the homolog of the mammalian Bmal1, show an exaggerated homeostatic response after short term sleep deprivation and begin to die if kept awake for 10h. In order to determine if disruptions in Bmal1 would alter sleep homeostasis, we studied BMAL1 KO mice. Because the homozygous BMAL1-/- mice suffer from several health problems, we focused our attention on the healthier BMAL1-/ heterogygotes; this strategy is supported by the observation that cyc01 is a dominant mutation for both homeostasis and lethality in the fly. In addition we examined sleep homeostasis in cyc02 flies, a cycle gene mutation that more closely resembles the genetic deletion in BMAL1 KO mice than that of cyc01 flies.
Methods: Wild type and BMAL1-/ male mice (4 to 6 months) were implanted for polysomnography using standard procedures and allowed to recover for 2 weeks. Sleep was recorded in mice maintained on either a 12:12 L:D schedule or in constant darkness. Following baseline, mice were sleep deprived for 6 and 12h by gentle handling and allowed to recover. Homozygous cyc02 mutants (3-5 day old) were evaluated using Trikinetics Activity Monitors. Sleep deprivation up to 12h in flies was achieved by gentle handling.
Results: WT and heterozygous BMAL1-/ mice exhibited similar amounts of nonREM sleep and REM sleep when maintained under both LD and constant darkness. In addition, both WT and BMAL1-/ mice responded similarly to 6 and 12h of sleep deprivation and the magnitude of the homeostatic response was not altered by the light schedule. Consistent with results obtained in the mice, flies that carried a mutation that more closely resembled the BMAL1 KO mice, cyc02, also showed a homeostatic response resembling wild type flies, with no signs of the lethality following 12h of sleep deprivation by gentle handling.
Conclusion: While cyc01 is a dominant mutation for sleep homeostasis in the fly, BMAL1-/ mice showed a normal response to both 6 and 12h of sleep deprivation. The genetic lesion in cyc01 flies may allow for a portion of the protein to be translated. Indeed, there is evidence to suggest that cyc01 behaves as a dominant-negative mutation. This is not the case for BMAL1 KO mice or cyc02 flies. Thus, it is not surprising that the homeostatic response of cyc02 mutants more closely resembles that of the BMAL1-/ mouse.

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Increased Expression of Hypothalamic Orexin mRNA is Associated with Spontaneous REM Sleep Suppression in Mice Deficient in the Interferon Type I Receptor

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Introduction: Type I interferons (IFNs) are up-regulated in viral infections and are well known for their antiviral activity. These IFNs and their receptor (RI) are spontaneously expressed at low levels in several regions of the normal brain in the absence of viral infections, but their functions are unknown. We have observed that spontaneous REMS, but not NREMS, is reduced 30-40% in mice with a targeted disruption in the IFN-RI gene (IFN-RI knockouts, or KOs) that disables the receptor. REMS suppression is most marked during the dark period, but extends into the early part of the light period. IFNs have been implicated in the suppression of orexin expression (through binding to an interferon-response element in the promoter of the prepro-orexin gene), and up-regulation of orexin can selectively suppress REMS. IFNs also share regulatory pathways with prolactin (PRL) and vasoactive intestinal peptide (VIP), neurohormones that are also implicated in the regulation of REMS. Therefore, we examined in IFN-RI KOs and their 129SvEv controls the expression of orexin, VIP and PRL genes in regions of the brain (hypothalamus and brainstem) known to be involved in REMS regulation.
Methods: Brains from IFN-RI KOs and their control mice, maintained on a 12:12 hr light cycle at 29 +/- 1 degree C, were removed from mice decapitated between 0900 and 1000 hr +/-(lights on at 0900 hr). Brainstems and hypothami were dissected out and rapidly frozen. RNA was extracted and cDNAs prepared by standard methods. Quantitative real-time RT-PCR (RT2-PCR) was employed to determine expression of mRNAs for orexin, PRL, VIP, and an antiviral gene known to be induced by IFNs via the RI, 2'5'-oligoadenylate synthase A (OAS). Gene expression levels in the IFN-RI mice were compared to 129SvEv control values, and expressed as fold-increase over controls.
Results: Hypothalamic orexin mRNA was expressed in IFN-RI mice at a level 2-fold higher than in controls ($n = 13$, $p < 0.003$). Hypothalamic PRL and VIP expression did not change compared to control levels. IFN-RI brainstem orexin, PRL and VIP mRNA levels were not different from controls. Endogenous OAS mRNA in the brainstem was significantly suppressed by 20-fold ($n = 13$, $p < 0.001$) in IFN-RI KOs compared to controls, confirming that the KO mice are functionally deficient in the RI receptor.
Conclusion: The substantial endogenous REMS suppression seen IFN-RI KO mice is associated with a significant increase in hypothalamic orexin mRNA, but expression of PRL and VIP is unchanged in the hypothalamus and brainstem of the KO mice.

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The Sequencing of Rat CREB-binding Protein (CBP) after its Up-regulation by Interleukin 1β

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Introduction: Creb-binding protein (CBP) is a co-transcriptional activator that regulates the activity of many genes, including cAMP response element binding protein (CREB). CREB is associated with the wake/sleep cycle because the activated phosphorylated form is elevated during the wake period. CBP participates in cAMP-regulated gene

expression by interacting with phosphorylated CREB. We found CBP mRNA elevated in hippocampal cell cultures following the administration of interleukin-1β (IL1β), as measured by differential display. To confirm this, the rat CBP gene was sequenced and real-time PCR primers developed to measure RNA expression levels following sleep deprivation and icv injection of IL1β.
Methods: Total RNA was isolated from rat hippocampal cells cultured with 10 ng/ml IL1β. Differential Display was performed by the Preferential Amplification of Coding Sequences (PACS) to identify coding sequence regions. The 4 ATG upstream primers and 4 double restriction site downstream primers were used in a combination of 16 reactions to identify up and down regulated genes. Bands of interest were excised from the gels, reamplified, cloned into the TOPO vector and PCR amplified with M13 forward and reverse primers to estimate product size. Inserts greater than 184 bp were counted as positive. The complete CBP gene was sequenced from rat visual cortex cDNA using primers based upon the mouse and human CBP sequence to produce overlapping 1.4 to 3 kb PCR products. Real-time PCR was used to measure CBP expression levels in samples following 8 hours sleep deprivation or icv injection of low and high doses of IL1β.
Results: Following differential display, 95 bands were identified as up regulated following IL1β treatment of hippocampal cells. Forty bands were cloned and sequenced. One 270 bp band was 96% homologous to the mouse CBP gene but because the published rat sequence had an error that produced a premature stop codon at base 1056, we sequenced the complete CBP gene. After correcting the error, the differential display CBP band matched the 4830 to 5099 base pair region of the completed rat sequence. The final sequence measures 8664 bases long and is 96.5% identical to the mouse and 89.0% identical to the human CBP sequences. This sequence translates to 2441 amino acids with a molecular weight of 265,295.8 daltons. Protein domains associated with CBP are identifiable, including the TAZ zinc finger, the TAZ 2 domain, the KIX domain, bromodomains and the Zinc binding domain. There was no change in brain CBP mRNA levels following sleep deprivation. The cortex of rats receiving high doses of icv IL1β showed greater than a 6-fold increase in CBP. The hypothalamus of these rats showed a 2.4-fold increase in CBP.
Conclusion: CBP may play a role in producing wakefulness.

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Elevated Brain Prolactin mRNA Levels in Mice with Suppressed Neuronal Nitric Oxide Synthase Activity
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Introduction: Nitric oxide (NO) and prolactin (PRL) are part of the humoral network that regulates rapid eye movement sleep (REMS). They likely exert their REMS-promoting actions through REMS regulatory circuits. Inhibition of neuronal nitric oxide synthase (nNOS) suppresses REMS. nNOS gene knockout (KO) mice have less REMS than their controls. Further, PRL up-regulates nNOS enzyme activity or nNOS protein expression. In addition, PRL activates nNOS-containing neurons in the laterodorsal tegmental nucleus (LDT) and thus induces NO release. However, it is unknown if NO affects PRL gene expression. In this study, we used real-time PCR to investigate the role of NO on PRL mRNA expression in 1) nNOS KO mice and 2) nNOS control mice treated with 7-nitro-indazole (7-NI), a relatively selective nNOS inhibitor.
Methods: Male 3-4 month old mice were purchased from Jackson Labs. The specific strains were nNOS KO mice (B6;129S4-Nos1tm1Plh) and nNOS control mice (B6129SF2/J). Animals were kept on a 12:12 h light/dark (lights on at 0800 hr and lights off at 2000 hr) cycle at 29 degrees C. 7-NI was purchased from Sigma. In experiment 1, nNOS KO mice and nNOS control mice (n=20) were sacrificed without treatment. In experiment 2, nNOS control mice (n =20) were divided into two groups. One group was injected with 7-NI (50 mg/kg per injection, intraperitoneal) suspended in peanut oil. The other group was injected with peanut oil. The injections began 3 days before sacrifice and were given 3 times a day at 0800 hr, 1400 hr and 2000 hr. On the day of sacrifice, the last injection was given at 1300 hr to ensure maximal nNOS inhibition at the time of sacrifice. All mice in experiment 1 and 2 were sacrificed at 1400 hr by cervical dislocation followed by decapitation. Immediately after sacrifice the brainstem and the hypothalamus were quickly dissected and placed in liquid nitrogen. Samples were further processed to extract mRNA and prepare cDNA. The real time PCR reactions were performed in triplicate. The fold-change between the mRNA expression levels of the experimental samples (KO mice or 7-NI treated mice) and the control samples (wild-type control mice or vehicle treated mice) were expressed in units of fold-change relative to the normalized controls. Gene expression levels were analyzed by unpaired Student t-test (KO vs. Control or 7-NI-treated vs. vehicle-treated). A significance level of $P < 0.05$ was accepted.
Results: Brainstem PRL mRNA levels in nNOS KO were about 4 times higher than those in nNOS control mice ($P<0.05$). After the 7-NI treatment, PRL mRNA expression was stimulated in the brainstem ($P<0.05$) and the hypothalamus ($P<0.05$) of nNOS control mice relative to that observed in the vehicle-treated nNOS control mice.
Conclusion: These results suggest that NO feeds back to inhibit the production of PRL mRNA. The PRL-NO interaction in the brainstem may play a role in REMS regulation.

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Systemic Administration of Interleukin-1 Beta or Tumor Necrosis Factor Alpha Increases Cytokine mRNA Levels in the Nucleus Tractus Solitarius and Somatosensory Cortex
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Introduction: Interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) are key elements in the brain cytokine network involved in non-rapid eye movement sleep (NREMS) regulation. Injection of IL-1β or TNFα into the peritoneal cavity increases NREMS in rats as well as brain cytokine mRNA levels. Vagotomy blocks these increases in NREMS and cytokine mRNA levels. Brain IL-1β mRNA and TNFα mRNA levels vary with sleep propensity. The aim of the current experiments was to determine the cytokine and neurotrophin mRNA responses in specific brain regions to peripheral administration of IL-1β or TNFα by means of real-time reverse transcription-polymerase chain reaction (PCR).
Methods: Male Sprague-Dawley rats (280 to 350 g) were injected intraperitoneally just prior to dark onset with a cytokine dose that previously was shown to be somnogenic. Three groups of rats were used. Group I received pyrogen-free saline (PFS); Group II received 0.5 μg/kg human recombinant IL-1β (R&D) and Group III received 100 μg/kg rat recombinant TNFα (R&D). Rats were sacrificed 2 h after ip injections. The nucleus tractus solitarius (NTS), a brain region that receives afferents from the vagus nerve, and the primary somatosensory cortex (SSctx) were quickly dissected and total RNA was extracted using Trizol

reagent. cDNA was prepared then analyzed for IL-1β, TNFα, IL6, IL10, BDNF, NGF, and somatostatin mRNAs using the real-time polymerase chain reaction technique.
Results: NTS IL-1β, IL6 and TNFα mRNAs increased significantly 2 hours after IL-1β injection (0.5 μg/kg ip; p = 0.04, 0.0002, 0.002, respectively). Two hours after TNFα treatment, NTS IL-1β, IL10 and TNFα mRNA increased significantly (p=0.0005, 0.03, 0.000004, respectively). SSctx IL-1β, IL6, TNFα and somatostatin mRNAs increased significantly 2 hours after IL-1β injection (p=0.01, 006, 0.025, 0.0003 respectively). Two hours after TNFα treatment, SSctx IL-1β, TNFα, and NGFβ mRNA increased significantly (p= 0.005, 0.0002, 0.02, respectively).
Conclusion: The results suggest that peripheral administration of IL-1β or TNFα up-regulates several cytokines in the nucleus tractus solitarius as well as in the cortex. Results are consistent with the hypotheses that a central cytokine network is involved in sleep regulation and that systemic cytokines influence central cytokine levels.

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Interleukin-1 beta Treatment Up-Regulates Hypothalamic Cytokines and Neurotrophin mRNAs in vivo and in vitro

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Introduction: Among the various sleep regulatory substances the cytokine, interleukin-1β (IL1β), is strongly implicated in non-rapid eye movement sleep (NREMS) regulation. Systemic or intracerebral injection of IL1β increases NREMS in various species including rats. Administration of anti-IL1β antibodies, the IL1β receptor antagonist or the soluble IL1β receptor inhibits spontaneous sleep and sleep rebound after sleep deprivation. Brain IL1β mRNA levels and cerebrospinal fluid (CSF) levels of IL1β protein correlate with sleep propensity. IL1β induces its own production as well as the production of several other substances implicated in sleep regulation including nerve growth factor (NGF) and tumor necrosis factor alpha (TNFα). IL1β receptors are found in cultured hypothalamic glutamate decarboxylase (GAD)-immunoreactive cells, a marker for GABAergic neurons. The aim of the current experiments was to determine cytokine, neurotrophin and GAD mRNA responses to IL1β treatment in vivo and in vitro using real-time reverse transcription-polymerase chain reaction (PCR).
Methods: For the in vivo experiment, male Sprague-Dawley rats (280 to 350 g) were implanted with a guide cannula in the lateral cerebral ventricle under anesthesia. Two groups of rats were used. Group I received pyrogen-free saline; Group II received 2.5 ng human recombinant IL1β 1 h before dark onset and were sacrificed 2 h later. The hypothalamus was dissected and frozen quickly. For the in vitro experiment, primary cultures of fetal hypothalamic neurons were prepared using poly l ornithine coated 6 well plates. Neurons were isolated from 21 day old fetuses and grown in Dulbeccos Modified Eagles Medium (DMEM) with 10 percent fetal calf serum. The medium was replaced every 2 days before use in experiments with serum free DMEM containing a defined serum substitute. The cultures were treated with IL1β [0, (n=12), 1 (n=12), 10 (n=12), or 100 ng/ml (n=12) for 2 hours. Total RNA was extracted using Trizol reagent and analyzed for IL1β, TNFα, NGF and GAD mRNAs using real-time PCR.
Results: Hypothalamic IL1β, TNFα, and NGF mRNAs increased significantly 2 h after IL1β treatment (2.5 ng icv) but GAD mRNA was not significantly altered. In the in vitro experiment, one way ANOVA indicated that IL1β (1,10, or 100 ng/ml doses) induced significant increases in TNFα, NGF and GAD mRNA levels. IL1β (10 ng/ml) induced a significant increase in IL1β mRNA compared with the control group, but was not significantly affected by the 1 ng/ml and 100 ng/ml IL1β treatments.
Conclusion: These results suggest that both in vivo and in vitro administration of IL1β up-regulates the synthesis of IL1β, TNFα, and NGF mRNAs.

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Synchronized SCN Cell Cultures Exhibit Rhythmic Expression of Per1 and TNF Alpha mRNAs

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Introduction: Network connectivity is the basis for the emergent properties of neuronal communities, and rhythms are an integral part of network function and integrity. Although many systems in mammalian organisms display circadian oscillation, there is only one master timekeeper, the SCN. This master clock adjusts circadian rhythms of the peripheral oscillators and the behavior of the organism as a whole including sleep. Because the period length of the SCN clock is not 24 hours, environmental cues are necessary to entrain the organism to the appropriate time of day. The SCN accomplishes this task by enforcing its environmentally-cued rhythm on the remainder of the organism. Although the mechanism of enforcement is unknown, a diffusible factor has been implicated previously in a culture system composed of a synchronized SCN derived immortal cell line (SCN2.2) and a co cultured non-SCN cell line. We report here the expression patterns of known sleep-regulatory substances in the SCN2.2 cell line in anticipation of identifying this diffusible substance.
Methods: Ten separate cultures of SCN2.2 cells were grown simultaneously to confluence on 60mm laminin-coated dishes in serum containing growth media. After 3 days at confluence, serum free conditions were applied for 2 days. A 50 percent serum shock of 2 hour duration was performed to induce circadian synchronization of the cultures. Following the return to serum-free conditions, single plates were harvested at 4 hour intervals using 1ml TRIzol reagent. RNA was purified by standard TRIzol protocol. Oligo-dT-primed SuperScript III reactions produced cDNA of consistent quality and quantity. Real-time PCR utilizing a BioRad I-Cycler and PlatinumUDG Supermix was performed to determine Per1, TNF alpha and CycA mRNA expressions. Samples were run in triplicate. CyclophilinA was used as an internal control to establish an expression baseline and to remove sample-to-sample variations in RNA recovery and reverse transcription efficiency. Standard deviation for triplicate samples ranged from 0.10 to 0.40 for TNF alpha (less than a single cycle), and from 0.06 to 0.23 for CyclophilinA (also less than a single cycle).
Results: Within 12 h of serum shock, Per1 mRNA levels increased by about 2 fold. By 24 h post serum, Per1 mRNA levels returned to baseline values. However, 12 h later at 36 h post serum, a 2 fold increase in Per1 mRNA was again observed, indicating that circadian rhythmicity was induced in these cells thereby confirming previous results. Changes in TNF alpha mRNA were much larger and were in antiphase to the Per1 mRNA changes. Thus the first peak of TNF alpha mRNA was observed at 4 h post shock; by 20 h, levels were at baseline values. At 24 h post serum shock TNF alpha mRNA again peaked and then returned to baseline values by 36 h post shock. Both peaks of TNF alpha mRNA were about 45 fold higher than baseline values.
Conclusion: TNFalpha mRNA displays a marked circadian rhythm in SCN2.2 cultures and is ideally poised to communicate and perhaps

enforce the SCN defined circadian time to peripheral oscillators.

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Hereditary Adenine Insertion Variant Of The Endothelin-1 Gene And Severity Of Obstructive Sleep Apnea

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Introduction: An association is suspected between endothelin-1, a potent vasoconstrictor, and obstructive sleep apnea (OSA), owing to the relationship between endothelin-1 and the major risk factors involved in OSA. Possible associations between certain genetic variations in the endothelin-1 gene and cardiovascular diseases have already been studied. We attempted to find out whether the endothelin-1 adenine insertion variant (+138/exon1 ins/del) is correlated with the severity of obstructive sleep apnea.
Methods: We studied a total of 391 consecutive men and women who were referred to our sleep laboratory with OSA. Inclusion criterion was an apnea/hypopnea index (AHI) > 5/h of sleep in the polysomnographic recording before treatment with nCPAP. All patients were thoroughly interviewed and filled out a questionnaire on their detailed medical history, risk factors for cardiovascular disease, sleep habits, and drug intake. Blood pressure was measured and blood samples for genotyping were taken. The volunteers gave their written informed consent to participate after receiving full written and verbal information. The local ethics committee approved the study. Genomic DNA was extracted from peripheral blood using a standard method. The endothelin-1 polymorphism +138/exon1 ins/del was detected using the method described previously by our working group. We employed the Kruskal-Wallis test to investigate a potential association of the genotypes with AHI. We further performed multiple linear regression analysis to analyze the functional relationship between AHI and potential influencing factors in addition to the genotype.
Results: Endothelin-1 insertion/deletion genotype distribution did not deviate significantly from the Hardy-Weinberg expectation (ins/ins 0.50, ins/del 0.42, del/del 0.07). Thus, the frequency of the adenine insertion/deletion for the group as a whole was 0,71/0,29. The clinical characteristics - age, gender, body mass index (BMI), diabetes, hyperlipidemia, coronary artery disease (CAD), hypertension (elevation of systolic or diastolic blood pressure, or history of hypertension), and smoking habits - of patient groups with various genotypes were comparable. The mean (± standard deviation) for AHI was lower in the group of the homozygous carriers of the deletion (28,4 ± 21,6/h sleep) than in the groups of heterozygous (35,6 ± 24,2/h sleep) and homozygous carriers (37,0 ± 24,7/h sleep) of the adenine insertion. But the adenine insertion/deletion genotypes were not significantly associated with AHI, neither with nor without adjustment for potential influencing factors.
Conclusion: The frequency of the adenine insertion/deletion for the group as a whole was comparable to the frequency for a large population-based control group in the ECTIM study (0,71/0,29). We did not find that this polymorphism of the EDN1 gene has a substantial effect on the severity of OSA.

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Sleep Rhythmicity And Homeostasis In Mice With Targeted Disruption Of mPeriod Genes

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Introduction: In mammals the timing of sleep and wakefulness is regulated by the suprachiasmatic nucleus (SCN) where a small set of genes interact to generate a transcriptional-translational feedback loop whose cycle length (period) coincides with the period of the Earth's rotation about its axis (Reppert and Weaver, Nature 418: 935, 2002). An important unanswered question is whether the same genes that regulate the circadian clock might have also evolved to regulate the amount of sleep and wakefulness. To date, sleep has been recorded in entrained and free-run condition only in mCry1 and mCry2 double-mutant mice (Wisor et al., BMC Neurosci 3: 20, 2002). Since mCry interacts with mPer to regulate circadian rhythms it is necessary to also investigate the role of the mPer genes on the rhythmic and homeostatic regulation of sleep.
Methods: Sleep recordings were made from mPer gene mutants and isogenic wild-type mice in entrained LD, after 6h sleep deprivation (ZT6-12) and weekly for five weeks in constant conditions (dark-dark). Core temperature was recorded continuously every two minutes and identified circadian rhythmicity. Throughout the experiment (almost 3 months) the mice were continuously tethered to the recording cable and there was no running wheel.
Results: In entrained conditions, when averaged over the 24h period, there were no significant differences in amount of time spent in waking, slow wave sleep (SWS) or REM sleep between mPer1 (n=6), mPer2 (n=9), mPer3 (n=8), mPer1-mPer2 (n=7) double mutants and wild-type (n=8) mice. However, the mPer2 and mPer1-mPer2 double mutants had earlier increases in temperature and wake, which is consistent with data from humans that mutation in the casein kinase I epsilon binding region of human hPer2 gene is associated with familial advanced sleep phase syndrome (Toh et al., Science 291: 1040, 2001). In response to 6h total sleep deprivation mice of all genotypes exhibited increased sleep drive, indicating an intact homeostatic response even in the absence of the mPer gene products. In free-run conditions (constant dark), the mPer1-mPer2 double mutants became arrhythmic, but they continued to maintain their sleep levels even after 36d in free-running conditions.
Conclusion: Mice that lose rhythmicity in constant conditions represent a good model to test the effects of specific genes on sleep homeostasis, since in these mice there is no effect of a circadian rhythm of activity. In contrast, in mice that show rhythmic activity in free-running conditions, sleep is likely to be influenced by both the central oscillator in the SCN as well as peripheral oscillators that respond to changes in metabolic states. The mPer 1-mPer2 double-mutant mice displayed arrhythmic behavior under free-run condition, with loss of circadian control over sleep, but they nevertheless maintained the amount of sleep, further indicating that the homeostatic regulation of sleep is independent of the circadian clock. mPer1 and mPer2 but not mPer3 represent key elements of the molecular clock in the SCN. Here we found that the mPer genes are not required for appropriate regulation of the daily amounts of waking, SWS or REM sleep.

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Hyperactivity and Altered Vigilance States in N-type Calcium Channel (CaV2.2) α1B Subunit Knockout Mice

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Introduction: The hypothalamic, thalamic, and mesencephalic expression pattern of the N-type CaV2.2 voltage-dependent calcium channel includes nuclei known to be involved in sleep/wake regulation, for example the locus coeruleus and dorsal raphe nuclei. We therefore characterized CaV2.2-/- mice for their spontaneous locomotor activity, vigilance state distribution, and EEG spectral properties.
Methods: For feeding studies, 20 week old male CaV2.2-/- mice (C57BL/6NCrj; Ino et al. 2001 Proc Natl Acad Sci USA 98:5323) and their wildtype littermates were habituated for one week to an automated food consumption monitor system before food and water intake were measured. At 29 weeks of age, spontaneous locomotor activity was measured under novel conditions (12 minutes, CT4) and habituated conditions (72 hours, three light cycles). Mice (22 weeks, n=6 per genotype) were also implanted with screwless lightweight EEG/EMG electrodes and allowed two weeks of recovery and habituation to recording conditions. Signals were recorded for 72 consecutive hours (three light cycles), archived in 20 sec epochs, and analyzed visually by two independent observers blinded to genotype. The EEG frequency distribution was analyzed by power spectral analysis from 1 to 32 Hz.
Results: No differences between genotypes were observed in access frequency or consumption of food and water. CaV2.2-/- mice under novel conditions, as well as under habituated conditions in the dark phase, showed significantly more spontaneous locomotor activity (increased by 20% and 95%, respectively) than their wildtype littermates. Vigilance state measurements revealed that, in the light phase, the number of REM sleep episodes decreased in CaV2.2-/- mice (27.3±0.7) compared to wildtype littermates (41.5±4.1) while the average episode duration increased (113±4 sec vs. 69±4 sec). This did not result in a net change of REM sleep time. However, REM sleep latency was increased in the light phase (11.3±0.8 min vs. 9.0±0.1 min, for CaV2.2-/- and wildtype, respectively). In CaV2.2-/- mice number of non-REM sleep and awake episodes also decreased during the light phase. No significant differences were observed between genotypes during dark phase, although we noted a tendency towards increased wakefulness and decreased non-REM sleep in CaV2.2-/- mice. EEG spectral power was increased in CaV2.2-/- mice during wakefulness and REM sleep, but decreased during non-REM sleep, when compared to EEG power spectra of wildtypes. Furthermore, the maximum peak in power during REM sleep shifted about 1 Hz from 8.5 Hz in wildtype to 7.5 Hz in CaV2.2-/- mice. These differences in spectral power between genotypes were specific for the respective vigilance states, because power averaged over all animals and recording periods was identical between genotypes.
Conclusion: CaV2.2-/- mice did not show any overt metabolic abnormalities, but were more active than their wildtype littermates. In the light phase, all vigilance states were less fragmented, indicating increased consolidation of sleep and decreased vigilance state transitions, particularly in REM sleep. This, together with the increased EEG power during wakefulness, suggests that the CaV2.2-/- mouse is more tonically alert and vigilant. This is the first report concerning a relationship between the N-type CaV2.2 channel and sleep-wake behavior (Beuckmann et al. 2003 JNeurosci 23:6793).

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Diurnal Variations Of CSF Hypocretin (HCRT) And Changes In Gene Expression As Detected By Microarrays In Young And Old Rats

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Introduction: The normal patterning of sleep architecture, sleep quality and sleep timing significantly deteriorates in both humans and animals with aging (Shiromani et al., Am J Physiol 278: R125-133, 2000). The fragmented daytime sleep, increased sleep during the normal wake-active period, and the early wake-up time might result from a shift in the phase position or amplitude of the rhythm of a wake promoting substance. To date, the best candidate is hypocretin (HCRT), but there is no data in animals that this system declines with aging. In elderly humans HCRT assayed at a single time point is not different compared to young subjects (Kanbayashi et al., Sleep. 25:337, 2002). However, because of the circadian variation in HCRT levels it is necessary to observe the overall diurnal rhythm of HCRT. Here we test the hypothesis in rats that there is a decline in HCRT with aging. We then use the gene-chip method to investigate whether such a decline can be attributed to loss of function of neurons in the lateral hypothalamus. Thus, the microarray is being used to confirm rather than explore.
Methods: CSF was collected from the cisterna magna of young (2 months, n= 9), middle age (12mos, n=10), and old (24 mos, n= 10) male F344 rats at 4h intervals, (beginning at ZT0, lights-on). CSF was collected once from each rat every 4 days at one ZT point. The rats were implanted (under anesthetic) with a transmitter to provide a continuous record of core body temperature rhythm. Separate group of similar age rats were killed and the lateral hypothalamus (LH) and the cortex were rapidly extracted for analysis of expression of 8000 genes using the Affymetrix chip. RT-PCR confirmed gene expression.
Results: Over a 24h period, old rats had significantly less CSF HCRT versus either middle age or young rats ($p<0.002$), but no significant difference in core temperature or gross locomotor activity. There was no difference in the phase position or amplitude of the HCRT rhythm, albeit sampling at hourly rather than the 4h intervals could reveal such a difference. There were no differences in the numbers of HCRT-immunoreactive neurons and in HCRT mRNA. Microarray gene analysis of the LH revealed in old rats a significant change, compared to LH of young rats or cortex of young or old rats, in genes involved in inflammation, neuronal signaling, and oxidative/lipid metabolism, suggesting a modification of the neuronal activity in the LH where the HCRT neurons are localized. Specifically, we found significantly decreased mRNA for the glutamate kainate receptor (GluR5) in the LH of old versus young rats.
Conclusion: HCRT neurons are driven by glutamate (Li et al., Neuron 36:1169, 2002) and our finding that there is a decline in the GluR5 receptor mRNA suggests that because of fewer GluR5 receptors the HCRT neurons might be less active. In addition, we found increased inflammation and decrease in genes regulating LH neuronal function, which suggest that there is an overall decline in function of LH neurons. This could result in HCRT neurons being less active which would result in less HCRT release. The decline in overall HCRT levels could then contribute to the increased sleep drive during normal wake-active periods in the elderly

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Genetic Influences in Self-Reported Symptoms of Obstructive Sleep Apnoea and Restless Legs: A Twin Study

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Introduction: Sleep disorders, such as obstructive sleep apnoea (OSA) and restless legs syndrome (RLS), are very common. The relative importance of genetic and non-genetic (environmental) influences on the symptomatology of these conditions has not been well studied. This study uses the twin design to examine this by evaluating OSA and RLS symptoms in monozygotic (MZ) and dizygotic (DZ) twins.
Methods: 6600 unselected female twin pairs, identified from a national volunteer twin register, were asked to complete a medical questionnaire. This questionnaire included questions on OSA and RLS symptoms, as well as questions on subject demographics, past medical history, smoking history and menopausal status.
Results: Responses were obtained from 4,503 individuals (68% response rate). A total of 1937 twin pairs were evaluable: 933 MZ pairs (mean (range) age 51 (20-76) years) and 1004 DZ pairs (age 51 (20-80) years). Concordance rates were higher for MZ than DZ twins for OSA and RLS symptoms. Multifactorial liability threshold modelling suggests that additive genetic effects combined with unique environmental factors provide the best model for OSA and RLS symptoms. Heritability for disruptive snoring, daytime sleepiness, restless legs, and legs jerking was estimated to be 52% (95% confidence interval 36-68%), 48% (37-58%), 54% (44-63%), and 60% (51-69%) respectively. These estimates dropped only slightly after adjustment for confounding influences on the symptoms of snoring and daytime sleepiness.
Conclusion: These results suggest a substantial genetic contribution to the symptomatology of OSA and RLS. More research is needed to identify the responsible genes, which may ultimately lead to new therapies.

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Region-Restricted Knockout of T-type Calcium Channel Cav3.1: Subcortical Neuron Bursts Stabilize NREM Sleep

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Introduction: During sleep, neurons do not become silent; instead, they fire in quasi-synchronous bursts. The function of this specialized form of sleep-related neuronal activity is unknown. We speculate that this bursting mode of activity serves to block sensory signals from reaching forebrain targets and thereby prevents arousal and helps maintain the sleep state.
Methods: Complete and region-restricted knockouts of T-type calcium channel Cav3.1 (alpha1G) were created using homologous recombination in C57/BL6 ES cells. LoxP sequences were placed within introns flanked exons 9-12 (floxed). Complete Cav3.1 knockout mice were created using mice expressing Cre recombinase in germline cells. Region-restricted deletions of Cav3.1 were created by breeding CAMKII-Cre (forebrain pyramidal neurons) or Kv3.2-Cre (thalamocortical neurons) transgenic mice with homozygous floxed Cav3.1 mice. These various genotypes were then analyzed using chronic EEG/EMG sleep and wake recordings.
Results: Complete deletion of Cav3.1 exons 9-12 abolished T-type calcium current and bursting in thalamic slices of dorsal lateral geniculate and lateral posterior thalamic nuclei in vitro. Furthermore, loss of thalamic bursting was associated with NREM sleep fragmentation: total NREM sleep and mean NREM bout duration were decreased. Cav3.1 mice had more short (20-120 s) and fewer long (300-500 s) NREM bouts. These NREM bouts were interrupted by frequent 20-40 s wake bouts. Consistent with a role for Cav3.1-mediated bursting in the production of sleep-related neuronal activity, the NREM EEG power spectrum was altered: power at 2.75-6.5 Hz was reduced, and power at 0.5-1.5 Hz was increased. EEG spectral power during transitional sleep spindles (11-19 Hz power during NREM proceeding REM) were also reduced in mutant mice. The major theta peak (6-8 Hz) during REM sleep was not significantly altered, but spectral power at 3.5-5.5 Hz was reduced in mutant mice. Using Cre/loxP region-restricted knockout techniques, we found that deletion of Cav3.1 from cortical pyramidal neurons recapitulated the REM EEG abnormality, but not the NREM sleep fragmentation or NREM EEG changes observed in complete Cav3.1 knockout mice. Novel thalamus-specific Cre recombinase transgenic mice were created using BAC homologous recombination and demonstrated to recombine loxP sites in thalamocortical projection neurons using an alkaline phoshatase reporter.
Conclusion: These data indicate that Cav3.1 T-type calcium channels play a critical role in bursting of thalamocortical neurons and in preventing arousals during NREM sleep. Such results may begin to explain how the brain maintains sleep in the face of arousing sensory stimuli.

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Identification of Sleep Regulatory Genes in a Sensitized Drosophila Mutant Using cDNA Microarrays

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Introduction: Flies mutant for the circadian clock gene cycle (cyc01) are extremely sensitive to sleep loss. These animals show an exaggerated homeostatic response after short term sleep deprivation and begin to die if kept awake for 10 hours. Because cycle is a transcription factor with few verified downstream targets, we initiated a cDNA microarray experiment in these sensitized mutants to identify the responsible regulatory pathways.
Methods: Sleep was evaluated for two days in three day old cyc01 females according to standard procedures. On day 3, flies were sleep deprived for 7 hrs using an automated sleep deprivation apparatus. Immediately following sleep deprivation, two thirds of the sleep deprived cyc01 flies and their untreated controls were frozen so that RNA could be extracted from whole heads. The remaining one third of the sleep deprived cyc01 flies and their untreated controls were monitored for an additional 24 hours to assay the size of the homeostatic response. Using this protocol, both gene expression and behavior could be evaluated in siblings that have been exposed to identical experimental manipulations. Eight microarray replicates were performed for each experimental group. Statistical differences between groups were identified using the Cyber-T Bayesian statistical framework (http://molgen.biol.rug.nl/cybert/). Each of these genes was then evaluated using real-time quantitative PCR (qPCR) to establish the validity of the microarray result. In addition, we evaluated the behavior of approximately 50 mutant lines representing 36 these loci of interest from the Bloomington Stock center.
Results: Statistical analysis of the microarray data indicated that approx-

imately 100 genes were differentially expressed. Approximately 70% of these genes subsequently displayed the expected expression profile using qPCR. Preliminary data indicate that 4 of these mutant lines showed statistical aberrations in total sleep time. Furthermore, several lines showed both increased and decreased sensitivity to sleep deprivation as measured by the size of the homeostatic response.
Conclusion: Using cDNA microarrays along with behavioral analysis we have begun to identify genes that modify sleep regulation in Drosophila. Ongoing experiments are being conducted to determine if these genes interact with the cyc01 mutation and to determine if homologous genes are modified in the rat following six hours of sleep deprivation.

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Evaluating A Drosophila Model Of Insomnia
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Introduction: If insomnia results, in part, from predisposing factors that cause either hyperarousal or misalignment of circadian rhythms with the sleep-wake cycle, then the identification of the underlying pathophysiological mechanisms should be feasible using genetic strategies. Using a population selection approach, we are developing a model of insomnia on a genetically tractable animal: Drosophila. We have isolated a population of flies that are both short sleepers and are sensitive to the removal of zeitgebers. We have further analysed their sleep structure in order to evaluate whether it could represent a useful model of insomnia.
Methods: Sleep structure (sleep time and distribution, sleep latency, sleep bout), locomoter activity, and responsiveness to environmental perturbations were evaluated using locomoter monitoring systems according to standard procedures. Three days old male and female wild type Canton S flies were monitored for four consecutive days at 25oC on a 12:12 L:D cycle. Flies that consistently demonstrated reduced sleep time were selected and bred over successive generations. The responsiveness of the selected flies to abrupt removal of zeitgebers was evaluated every 15th generation by transferring them to DD or LL conditions (constant darkness or constant light). Microarray experiments in the lab have identified several genes whose expression is highly up-regulated in response to sleep deprivation. The expression of these marker genes was determined in selected flies using standard QPCR methods on adult head RNA extracts.
Results: Total sleep time has been reduced from 700 to 200min/day by the selection process over 60 generations. This is a consequence of a reduction in the length, but not the number of sleep bouts (which remains similar to control flies). Sleep latency is dramatically increased in the selected flies (from 22 ± 2 min to 218 ± 53 minutes). When light zeitgebers are abruptly removed, selected flies show a further and substantial decrease in total sleep time; a result not observed in control flies. In order to assess sleep drive in these animals, we assessed the expression of gene markers of sleep deprivation: these genes are upregulated in the selected flies when compared to wild type controls, suggesting that sleep reduction in the selected flies is correlated with increased sleep drive. In addition to changes in sleep architecture, selection significantly increased the intensity of waking locomoter activity during both light an dark periods.
Conclusion: A common sleep complaint, insomnia is a complex disorder, manifested in response to environmental and/or to predisposing factors. By selecting over several generations flies that sleep significantly less than average, we have isolated a population of animals that show an array of phenotypes associated with insomnia: increase in sleep latency, shorter sleep bouts, hyperarousal, and gene expression profiles suggestive of sleep deprivation. Future investigations will aim at identifying the causes of sleep reduction in these animals and to assess its consequences on their health.

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APOE4 Genotype and Sleep Apnea in Alzheimers Disease: Initial Studies
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Introduction: Some recent studies have suggested that the apolipoprotein epsilon 4 (APOE4) genotype may predispose to sleep apnea (Kadotani et al, JAMA 2001; 285: 2888-90), however this association may vary among populations depending on age, racial composition or other undetermined factors. The APOE4 genotype was initially shown to be related to late-onset Alzheimers Disease (AD) with heterozygotes carrying elevated risk of 2 to 4 times the risk of non-carriers and homozygotes demonstrating as much as a 30-fold higher risk. In this study we present initial data from a study of sleep apnea in well-characterized, probable AD patients examining the effects of APOE4 genotype on sleep apnea expression in this patient group.
Methods: Patients were 33 individuals with probable AD, as defined using NINDS/ADRDA criteria. Of these individuals, genotyping was available on 23 (X age = 73.1; SD = 10.6; 16 M, 7 W). Genotyping was performed using polymerase chain reaction-RFLP technique with polyacrylamide gel electrophoresis. Mean Mini-Mental State Exam of the APOE patients was 24.5 (SD = 3.8). Sleep apnea was recorded in lab with the Embletta PDS system.
Results: Overall RDI for the sample was 12.0 events/hr (SD = 9.2) (range 0 – 34.4). Mean Desaturation Index (>/= 4%) was 8.3 events/hr (SD = 5.6) (range 0 – 20.7), and mean cumulative time < 90% was 10.2 mins (SD = 16.7) (range 0 – 70.8 mins). Of 9 patients positive for the E4 allele, 6 (66.7%) demonstrated a Respiratory Disturbance Index > 10.0, whereas for those without this allele, only 5 of 14 (35.7%) had RDI > 10.0. Because of the small N, the Odds Ratio was non-significant (OR = 3.6, 95% CI = 0.6 – 21.0).
Conclusion: Associations between sleep apnea and the APOE4 genotype in patients with probable AD remain unproven at this juncture, though our sample was constituted almost entirely by heterozygotes (8/9 patients), and inclusion of homozygotes may confer greater risk. If such associations can be confirmed, the role of this genotype as a common marker for both AD and sleep apnea may fundamentally reflect a predisposition to cerebrovascular disease, increasingly recognized as a risk factor for all forms of dementia in late life.

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Exploration and Sleep in RIM1α Knockout (KO) Mice Following Exposure to Novel Environments
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Introduction: Rab3A and RIM1α, a molecular effector of Rab3A, are

release machinery proteins that regulate neurotransmitter release. Rab3A KO and RIM1α KO mice display partially overlapping phenotypes in presynaptic plasticity, but RIM1α KO mice have deficits on certain learning tasks that are not exhibited by Rab3A KO mice. Rab3A KO mice also have altered activity and sleep homeostatic responses compared to controls. To investigate whether the RIM1α pathway might be involved in the regulation of activity and sleep, we conducted studies in RIM1α KO and wildtype (WT) mice. We also examined behavior and sleep in RIM1α KO and WT mice exposed to environmental novelty in the form of cage change (CC) and an open field (OF).

Methods: The subjects were three-month-old male RIM1α KO (n=7) and WT (n=7) mice. Locomotion, rearing and center time were measured with photobeams for 30 min in a standard OF and for an additional 30 min with a novel object (NO) placed in the center of the OF. The OF data were analyzed in six 5-min segments (blocks 1-6). Afterwards, the mice were implanted with transmitters for recording EEG and activity via telemetry. After recovery from surgery, baseline sleep was recorded for 48 h. Sleep was also examined for 22 h (10 h in light and 12 h in dark) following CC and following 30 min OF exposure. The CC and OF sleep data were analyzed in two 5-h light period segments (blocks 1-2) and two 6-h dark period segments (blocks 3-4). Comparisons across groups or conditions were conducted with t-tests.

Results: Compared to WT, KO mice in the OF displayed significantly greater locomotion and rearing during blocks 4-6 and with the NO placed in OF showed more locomotion during all blocks and longer center time in blocks 5-6. KO mice had less total baseline NREM (KO: 688±58; WT: 809±46) with similar light period NREM (KO: 458±26; WT: 462±32) and significantly different dark period NREM (KO: 230±37; WT: 347±16, $p < 0.009$). REM did not significantly differ in total baseline amounts (KO: 41±8; WT: 50±10) or in the light or dark phases. Following CC, KO mice showed significant reductions during block 1 in both NREM (Base: 189.9±9.4; CC: 116.2±28.8) and REM (Base: 14.3±3.2; CC: 4.7±0.8). After CC, WT mice had reduced NREM (Base: 195±9.5; CC: 166±15.2) during block 1 and increased REM (Base: 16±4.0; CC: 24.4±3.1) during block 2. After OF exposure, KO mice exhibited significantly increased REM (Base: 10.2±3.4; OF: 20.3±2.8) during block 2 and WT mice showed decreased NREM (Base: 195±9.5; OF: 166±15.2) during block 1.

Conclusion: These data indicate that the RIM1α gene may be involved in regulating basal sleep and in mediating the influence of environmental stimuli on activity and sleep. The difference in basal NREM in Rab3A KO mice (greater) and RIM1α KO mice (lesser) compared to their respective WT controls suggests that these two genes exert their effect in sleep through at least partially independent molecular pathways. Future studies should investigate whether they also differ with respect to behavioral and sleep responses to novelty and in homeostatic regulation of sleep.

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Molecular Correlates of Migratory Sleeplessness in the White-Crowned Sparrow

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Introduction: Recent evidence from our laboratory demonstrates that White-crowned sparrows markedly reduce sleep during migration. Despite restricting sleep, these birds function physically and cognitively at a high level during the migratory period. In the wild, they remain proficient at flying and navigating at night, as well as detecting prey and predators in unfamiliar habitats during the day. Moreover, unpublished operant experiments from our laboratory support the notion that songbirds do not suffer the typical functional consequences of sleep deprivation. Analyses of gene expression in the rat and fruit fly indicate that several transcripts are differentially expressed in relation to sleep, wakefulness and sleep deprivation. The aim of this study was to identify changes in gene expression in the forebrain of the migratory White-crowned sparrow during and after the migratory period. Using this model of natural sleep deprivation will allow us to ascertain whether there are fundamental molecular differences between this sponateous sleep deprivation and enforced deprivation in the rodent brain. In addition, this analysis has the potential to identify genes that might aid these animals in maintaining normal cognitive performance despite marked sleep reduction.

Methods: Male and female migratory White-crowned sparrows (Z.l gambelii, n=6, LD 16:8) in the migratory period or in the post migratory period (n=6, SD 10:14) were matched for photoperiodic conditions and amount of time spontaneously awake to male and female birds of a non-migratory subspecies of White-crowned sparrow (Z.l nuttalli, n=6/group). Animals were sacrificed between 1:00 and 3:00 PM after being spontaneously awake for at least five hours. The migratory birds had been in the migratory state for approximately five days prior to sacrifice. mRNA differential display (DD) was used to perform a systematic analysis of gene expression in the avian forebrain. Total RNA (2ug) was purified from the right forebrain of each animal, reverse transcribed, and amplified by PCR using one out of the three 3' anchor primers used for reverse transcription and one out of twenty 5' arbitrary primers. Radiolabeled PCR products were separated on denaturing polyacrylamide gels and differentially expressed bands were quantified using a phosphorimager. The mean density within and among conditions was evaluated by ANOVA followed by Bonferroni correction.

Results: Thus far, we have screened an estimated 9,000 transcripts. We have identified a total of seven mRNA transcripts that appear selectively altered during in the migratory subspecies, including three transcripts with higher mRNA levels during migration, and four with higher mRNA levels in the non-migratory state. In addition, we have identified two species-specific transcripts and seven transcripts whose expression is modulated by time of year.

Conclusion: An extensive screening of gene expression in the forebrain of groups of migratory and non-migratory subspecies of sparrows has yeiled a small number of targe genes altered in each state. Despite studying wild-caught birds from two different species, there has been a remarkable degree of consistency in gene expression across birds and across states.

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REM Sleep And Behavioral Differences In Mice Lacking Norepinephrine And Orexin

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Introduction: Noradrenergic signaling has long been implicated in the regulation of sleep/wake states. Although we have previously not found differences in amounts of sleep wake states between norepinephrine-deficient (NE-deficient) mice and controls, we have shown that the NE-deficient mice have a consistently shorter sleep latency after an injection saline. Previous experiments have also shown that NE-deficient mice do not respond to an injection of a low dose of amphetamine (1.0 mg/kg), whereas control animals show increased wakefulness. Orexin-deficient (OX-deficient) mice are narcoleptic, and have a severe phenotype characterized by increased REM sleep, fragmented sleep, and frequent

behavioral arrests at night. Both of these mutants show sleep initiation abnormalities, and both OX and NE are considered to be "wake-promoting". In an attempt to determine if the narcoleptic phenotype would be more severe in the absence of NE, and if the decrease in sleep latency in the NE-deficient mice would be more pronounced without OX, we bred these two mutants together to create mice deficient in both neurotransmitters.

Methods: Mice heterozygous for the mutant orexin allele were obtained (M. Yanagisawa, U of TX, Dallas) and bred with heterozygous NE-deficient mice, to eventually create NE-deficient mice, OX-deficient mice, NE/OX-deficient mice, and wild type (WT) mice. There were 8 to 9 mice per group. Sleep/wake states for the day, night, and 24 hours were determined from EEG/EMG recordings. Sleep latency was determined from EEG/EMG recordings following injections of saline and 1.0 mg/kg amphetamine. In addition, infrared videorecording was done for the first 4 hr of the beginning of the dark period, and behavioral arrests were scored from the tapes.

Results: At night, there were no significant differences in sleep/wake states between the NE/OX-deficient mice and the OX-deficient mice. The OX-deficient mice exhibited the expected differences in wake (less) and REM sleep (more) as shown in previous reports, as compared to WT mice. During the day, the NE/OX-deficient mice had fewer wake bouts ($p<.01$), fewer NREM bouts ($p<.01$) and more total REM sleep ($p<.05$) than the OX-deficient mice. There were no differences in total time spent in Wake, NREM or REM between the OX-deficient mice and the WT mice during the day. Over the 24-hr period, both the NE/OX-deficient mice and the OX-deficient mice had significantly more REM sleep than the WT mice ($p<.05$), but these were not different from each other. For sleep latency, the NE/OX-deficient mice and the NE-deficient mice both had significantly shorter sleep latencies after the saline and amphetamine injections ($p<.05$, $p<.001$). There was no significant difference between the NE/OX-deficient mice and the OX-deficient mice with respect to the number of behavioral arrests over the 4 hr of videorecording, however the NE/OX-deficient mice showed behavioral arrests that were significantly shorter in duration ($p<.01$).

Conclusion: The addition of the NE-deficiency to the OX-deficient phenotype resulted in an increase in REM sleep during the daytime. This was unexpected because there were no differences in REM sleep in the NE-deficient mice compared to the WT mice in any REM sleep measure in any time period. One interpretation is that OX compensates for NE in the NE-deficient mice, which enables them to maintain normal levels of REM sleep during the part of the day they sleep the most. For the sleep latency differences, the NE/OX-deficient mice behaved similarly to the NE-deficient mice after an injection of saline or amphetamine (short sleep latency), implying that OX is not contributing to wake promotion under these circumstances. The addition of the NE-deficiency to the OX-deficient phenotype also resulted in a shorter average duration of their behavioral arrests, which was also unexpected. Additional night-time videorecording of these mutant mice in a novel environment is underway.

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Genetic and Environmental Influences on Insomnia and Daytime Sleepiness in US Twins

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Introduction: Estimates of the heritability of subjective sleep problems range from 28 to 42% for insomnia and 38 to 40% for sleepiness, with most twin studies being performed in foreign countries, such as Finland, Australia or Italy. The few that have been performed in the United States involve highly selected populations of older adult male veterans. We sought a better understanding of the heritability of insomnia and sleepiness by studying a population-based sample of monozygotic and dizygotic twins residing in the United States.

Methods: We surveyed adult twins 18 years of age or older in the University of Washington Twin Registry. Data were collected on insomnia and daytime sleepiness from these twin pairs by asking them two questions: 1) how often do you have difficulty falling asleep or staying asleep and, 2) how often do you fall asleep during the day against your will? The monozygotic and dizygotic twin correlations for these two phenotypes were used in a classical twin study analysis to estimate the influence of genes and the environment on insomnia and sleepiness.

Results: The 500 monozygotic and 355 dizygotic twins who provided information were, on average, 29 years old with 49% being female. The overall prevalence of insomnia was 18.6% and for daytime sleepiness it was 3.4%. Twin correlations for insomnia were 0.64 in monozygotic pairs and 0.18 in dizygotic pairs. This resulted in a significant additive genetic influence for insomnia with a heritability estimate of 62% ($p = 0.001$); there was no effect of common environment ($p = 0.99$). For daytime sleepiness the twin correlations were 0.31 in monozygotic and 0.27 in dizygotic pairs. The heritability estimate for daytime sleepiness was 8% ($p = 0.75$); common environmental effects accounted for 23% ($p = 0.24$) of the liability to daytime sleepiness.

Conclusion: The genetic influence on subjective sleep problems varies depending on the phenotype examined. Insomnia appears to be under strong genetic control while genetic factors have only a small influence on daytime sleepiness. The heritability estimate for insomnia was larger than that reported in other studies and the weak genetic influence on sleepiness was contrary to published reports in highly selected populations.

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Genetic Dissection of Hypocretin and Histamine Systems in the Developing Zebrafish through Random Mutagenesis

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Introduction: Hypocretin and histamine are key neurotransmitters in the control of sleep and wakefulness. Hypocretin is involved in the sleep disorder narcolepsy, and it regulates histamine, an important monoaminergic regulator of wakefulness. The rate-limiting enzyme for production of histamine is histidine decarboxylase (HDC). We are examining the mRNA expression of HDC and hypocretin in zebrafish (Danio rerio), an animal model ideally suited for developmental and genetics research. As part of an ongoing mutagenesis screen, we will employ forward genetic approaches to discover functional regulators of sleep and wakefulness systems.

Methods: Digoxigenin-conjugated riboprobes complimentary to zebrafish HDC and hypocretin mRNA were hybridized to wholemount wild-type (Scientific Hatcheries) larval zebrafish and immunohistochemically visualized. Sense probes served as a control. Larvae were 3 to 7 days post-fertilization. A three-generation genetic screen for mutant hypocretin or HDC expression is in progress. Mixed background (AB, Tü, TL, and WIK) fish were chemically mutagenized with N-Ethyl-N-nitrosourea (ENU); 200 F2 families are being screened for recessive mutant phenotypes. For each family, progeny from at least 3 independent F2 breeding pairs are analyzed. These F3 progeny ($n \geq 16$ larvae/pair) are collected and analyzed by high-throughput in situ hybridization.

Results: Hypocretin signal was detected in a loosely-clustered bilateral

group of cells in the ventral diencephalon. HDC signal was detected in a scattered bilateral group of cells in the ventral, caudal diencephalon. Sense control probes yielded no signal. To date, screening for putative hypocretin mutants has been performed on 97 F2 families, and screening for HDC mutants has been performed on 79 F2 families. A recessive mutation was identified in one family (F2W487) thus far; mutant larvae display little or no HDC.
Conclusion: These results indicate that both HDC and hypocretin mRNAs are expressed in developing zebrafish, beginning by at least 3 days post-fertilization, in a pattern and location similar to that observed in mammals. Our data suggest that zebrafish may be employed as a useful animal model to study hypocretin and histamine systems in vertebrates, and they complement other experiments performed in our laboratory using immunohistochemistry in larval and adult zebrafish. Genome-wide mutagenesis of the developing zebrafish is a viable approach to discovering genes related to sleep and wakefulness. Genes for other sleep-related proteins may be incorporated into this screen in the future.

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Association of the Length Polymorphism in the Per3 Gene with Phase Delayed Sleep Syndrome: Is There an Effect of Latitude?
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Introduction: In the recent years great advances in understanding the molecular basis of circadian rhythmicity have been achieved. Animal studies have been shown mutations and polymorphisms regulating normal and pathological sleep. Delayed Sleep Phase Syndrome (DSPS) is a sleep disorder characterized by a delayed sleep onset, resulting in insomnia and difficulties to wake up in the morning. Ebisawa et al. (2001), have analyzed the structure of a Per3 gene and reported an association with DSPS. Archer et al. (2003), analyzed a length polymorphism (54 bp repeat region) in this same gene and reported an association of the 4-repeat allele with DSPS, these both studies were done in high latitudes in the north hemisphere. Thus, the aim of the present study is to verify a possible association between the Per3 length polymorphism described by Archer (2003) with DSPS in a different latitude in the south hemisphere.
Methods: Participated in the study seventeen DSPS patients, a population selected for diurnal preference, and a sample of the Brazilian population no scored for Horne-Ostberg questionnarie(H-O). The Per3 length polymorphism genotyping was done according Ebisawa et al. (2001) and Archer et al. (2003). The frequencies in each group were compared using the x2test, the p was set at 0.05.
Results: We have found a significant higher frequency of the 5-repeat allele in the DSPS patients group (0.56) when compared with the general population (0.34) x2=5.72, p=0.017 . We also observed an association of this polymorphism with diurnal preference with a higher frequency of the 5-repeat allele in the morning group (0.40) compared with evening group (0.23) x2=6.47, df=2, p=0.039 .
Conclusion: We have confirmed the association of the Per3 length polymorphism with extreme diurnal preference reported by Archer et al. (2003). But unexpectedly we have found a higher 5-repeat allele frequency in the DSPS patients group, contrary of Archer's data. These differences could be due to the latitude where the studies were done.

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Sleep and Ventilatory Behavior in A/J and C57BL/6J Mouse Strains
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Introduction: Human twin studies indicate that the pattern of breathing during wakefulness as well as in slow wave sleep (SWS) may be inherited. Our intent was to test further this hypothesis in in-bred mouse strains known to vary in breathing patterns during wakefulness (Tankersley et al, 1997; Han et al 2002) to determine if differences persisted into REM sleep as well as into SWS.
Methods: Studies were performed in C57BL/6J (B6; Jackson Laboratory), and two A/J strains (A/J Jackson and A/J Harlan) separated as commercial colonies since 1981. Recordings of ventilatory behavior (respiratory frequency, tidal volume, minute ventilation, mean inspiratory flow, and duty cycle) and of metabolism were performed by the plethsmography method with animals instrumented to record state (EEG and EMG) and heart rate.
Results: In all strains there were significant reductions in minute ventilation and CO2 production with transitions to SWS and REM sleep. However, the awake rapid shallow breathing pattern of the B6 relative to both A/J strains was preserved during sleep despite similar effects of state on metabolism and heart rate. In sleep, there were quantitative qualitative differences in breathing frequency in the B6 relative to the A/J strains; compared to SWS in REM sleep breathing frequency in the B6 rose while in the A/J strains it fell. The A/J Jackson and A/J Harlan differed quantitatively, with the former having a slower frequency and trend towards a higher tidal volume. In regard to heart rate, there were differences among strains, and overall heart rate varied inversely with frequency but directly with tidal volume. Heart rate in relation to breathing frequency was distinctly different among strains ($p<0.01$) in both SWS and REM sleep. The coefficient of variation was similar among strains, and was greater for tidal volume, mean inspiratory flow, and heart rate, than for measures for respiratory rate and duty cycle.
Conclusion: We conclude that genetic background strongly affects features of breathing rate and ventilatory behavior despite broad changes in state and heart rate. Furthermore, quantitative differences occur between the same strains maintained in different colonies suggesting an impact of genetic drift or environment on sleep-related phenotypes.

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An Autosomal Semi-dominant or Dominant Mutation Increases the Amount of Active Sleep in Neonatal Mice
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Introduction: In an intensive mutagenesis program, we have examined behavioral sleep-wake states in over 5,000 offspring of male mice that were injected with the chemical mutagen ENU to induce random mutations in the germ lines. One animal identified early in the screen, with an unusually large amount of active sleep as a neonate, has subsequently given rise to 4 generations of mice showing this altered phenotype in

about 50% of the offspring, indicating that a single gene mutation, inherited in a dominant or semi-dominant fashion, has led to a large increase in both the total amount of active sleep as well as the duration of active sleep bouts.
Methods: We examined the behavioral states of wake (W), quiet sleep (QS) and active sleep (AS) by recording EMG activity with temporary fixed electrodes for 2-3 hour periods in 9-10 day old pups (G1 animals) that were the offspring of mutagenized C57BL/6J male mice. One of the animals selected for further study, 1GO598, showed an abnormally large amount of active sleep that was 2.6 SD from the mean of all the animals tested prior to this animal's recording. The measured sleep parameters that were analyzed in the pups were: W%, QS%, AS%, number and mean duration of bouts for each behavioral state.
Results: 1GO598, a male, was mated to wild-type C57BL/6J female mice to create 32 G2 pups. Ten of these pups with a mean AS amount of 81.6 ± 4.1% (mean for our entire G1 data base = 55.3 ± 12.5% for 4,824 animals) were bred to produce G3 and subsequently G4 generation animals. In the G4 generation, 19 of 36 animals showed a mean AS time of 81.6% (2.1 SD from the mean) while the remaining animals had a mean of 66.9%. While less than 1 in a thousand animals in our data base showed more than 85% AS, in the 1GO598 line, 8% showed this drastic increase in AS time. Similarly, while less than our 1% of the animals in our data base showed AS time of greater than 80%, we have found 22% of the 1GO598 line with this amount. Further analysis of all the offspring from this line revealed that the mean duration or length of each AS bout (dbAS) was even a better discriminator of 1G0598 mutant animals from either wild-type or their siblings not carrying the mutant alleles. Indeed, the mean dbAS was 1.46 min in the founder animal, 3.3 SD from the mean (0.68 min ± 0.24) of all 4,824 animals in the data base. The 19 of 36 animals in the G4 generation showing high amounts of total AS had a mean dbAS of 1.85 ± 0.45 minutes, a value 4.9 SD from the mean.
Conclusion: We have identified a mutant line of animals carrying a dominant or semi-dominant mutation that increases both the total amount of AS, as well as AS bout duration in neonatal animals. Genetic mapping of this mutation is underway. Homozygous mutant animals are being generated. As an adult, male mice of the 1GO598 line sleep 1-2 hours more than wild-type animals.

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Novel Mutagenesis Model to Screen and Discover Genes that Affect the Seep-wake Cycle

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Introduction: Considerable evidence supports a role for genetic factors in the regulation of mammalian sleep and wakefulness as well as in the pathogenesis of sleep disorders, although at present, no major regulatory genes have been identified. We are taking a forward genetic approach using a chemical mutagen, N-ethyl-N-nitrosourea (ENU), to induce random mutations in the germ line of male mice and then screening the offspring of these animals for abnormal behavior sleep and wake states that are due to a semi-dominant or dominant mutation.
Methods: In order to carry out a mutagenesis program it is necessary to screen a large number of animals for phenotypic observations that are relatively easy and inexpensive to measure. We did not believe it was feasible to use such an approach if it was necessary to monitor EEG/EMG sleep in adult animals. Therefore, we developed a novel mutagenesis and phenotypic screening program testing first generation (G1) offspring (from ENU mutagenized C57BL/6J male mice) at 9-10 days of age in order to identify outliers, called putative mutants (putants), on any of a variety of sleep-wake parameters. In pups, the behavioral states of wake (W), quiet sleep (QS) and active sleep (AS) were differentiated by recording EMG activity with temporary fixed electrodes for a 2-3 hour period. G1 putant animals were then bred to wild-type animals to determine if the abnormal sleep-wake phenotype was genetically transmitted in subsequent generations (i.e. G2-G4 generations).
Results: We tested 5,144 G1 offspring from 756 mutagenized male mice over a 10-month period. We identified 181 animals with an "unusual" sleep-wake phenotype from the 4,824 "scorable" EMG recordings (3.8%). After testing pup sleep in 2,324 G2 offspring of the putant G1 animals, we selected 68 lines for further breeding to the G3 generation. To date we have examined sleep in 1,647 G3 and 492 G4 pups, and have currently identified 13 lines of animals that appear to have a genetically transmitted alteration in pup sleep-wake phenotype, 4 other lines are still in the early G2 testing phase. Adult sleep is being tested in the most promising lead lines of animals, and crosses are being set up to generate homozygous mutant animals.
Conclusion: We have generated a number of lines of animals that appear to be carrying a single gene mutation that alters the total amount or pattern of active sleep, quiet sleep and/or wake in neonatal mice with at least some of these animals also showing altered sleep-wake phenotype as adults. These animals should prove to be extremely valuable in studying sleep and wake mechanisms during development and into adulthood, as well as in uncovering novel genes/alleles that are involved in the physiology and pathophysiology of sleep-wake regulatory mechanisms.

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Effects Of Sleep Deprivation In The FAAH Knockout Mice

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Introduction: Fatty acid amides (FAAs) have been implicated in the regulatory mechanisms of sleep. However, due to their prompt catabolism by fatty acid amide hydrolase (FAAH), their behavioral effects, in vivo, are transient. Herein we demonstrate that in the absence of FAAH, the hypnogenic FAAs induce an increase in the duration of sleep. We also have characterized the sleep-wake patterns in FAAH knockout mice before and after sleep deprivation (SD).
Methods: Adult homozygote FAAH KO mice (n= 7), heterozygote FAAH KO mice (n=7) and non-transgenic mice (n=7) were anesthetized with 1.0 % halothane and implanted for chronic sleep recordings. Two weeks after surgery, mice were habituated to recording conditions for 48 h followed by 24 hrs of baseline recording. After baseline recording was completed, mice were sleep deprived for 8 hr, followed by a recovery recording for 16 hr. SleepSign software (Kissei Comtec America, Irvine, CA) was used to score the EEG, and three stages were determined: wakefulness (W), slow-wave sleep (SWS), and rapid eye movement (REM) sleep. Results were statistically analyzed using an ANOVA and then a post-hoc Sheffe test.
Results: Our results demonstrate that homozygote FAAH KO mice spent more time in SWS than do control littermates during the light period (CT-0/CT-12) [$p < 0.05$], In addition, we found a reduced rebound in the amount of SWS in homozygote FAAH KO mice after SD, together with a long-lasting increase in the levels of slow wave EEG frequencies compared to littermate controls.
Conclusion: Our results support the role of FAAH as an important reg-

ulator of the hypnogenic processes associated to FAAs in vivo.

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Pharmacogenomics Of Sleep-Promoting Drugs In Zebrafish

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Introduction: Mutilple agents have been used to induce sleep in humans including GABAergic drugs such as benzodiazepines and barbiturates, anti-histamines and sedative antidepressants. The mode of action of these drugs is only partially known and inter-individual differences in drug responses well established. We are using Zebrafish to identify genes that may modulate hypnotic drug responses. A collection of pharmaceutical compounds belonging to the classes mentioned above was tested in preparation for an ENU mutagenesis behavioral screen. We found that some but not all sleep-promoting agents were able to decrease the spontaneous locomotor activity and, at high doses to induce a sleep-like state in Zebrafish larvae.
Methods: Zebrafish larvae, 1 to 2 weeks old were maintained at 28°C under 14:10 light:dark cycle and fed until the day of experiment. Direct exposure experiments: Zebrafish in the treatment and control groups (n= 20) were placed into wells containing untreated water and allowed to habituate to their new environment for 30 minutes prior to testing. Behavioral responses (single touch test and swimming behavior) were studied following single 1-hour exposure to sleep-promoting drugs (GABAergic, histaminergic, adrenergic drugs) at different doses (doses ranging from 10-5M to 10-3M). Vehicle alone was used as a control. When possible, the effect of concomitant antagonist/agonist administration was also investigated to verify specificity. Microinjection experiments: Zebrafish larvae 5-7 days post fertilization were anesthetized with tricaine and mounted into methylcellulose while microinjections were performed. Several nanoliters of each compound (10-5 to 10-2 M) were injected intracerebroventricularly (icv) or intravascularly. Rhodamine-labeled dextran was used as a tracer to verify injection. Vehicle alone was injected as a control. For reversal/antagonism experiments, larvae were first treated by immersion with one drug for 1 hour then injected with the corresponding antagonist/agonist icv.
Results: Barbiturates, benzodiazepines and antihistaminic were all shown to induce a reversible sleep-like state in zebrafish larvae in a dose-dependent manner. As drug concentrations increased, swimming and behavior were increasingly altered. First a loss of proper balance was observed, with the fish making visible efforts to maintain an upright position using slow and aimless movements, then spontaneous movements were reduced and the fish stayed immobile for long periods of time. At higher doses, a complete absence of swimming was noticed but fish were still responsive to a single touch test, a measure of arousal response. A failure to respond to external stimulus was finally observed at the highest doses (anesthesia plan). The icv administration of benzodiazepine antagonist was able to reverse the behavioral effects of benzodiazepines.
Conclusion: Our study demonstrates that the Zebrafish model can be used to study the effects of medications on behavior. We are now using ENU-mutagenesis to search for genetic alterations that will either increase or decrease sensitivity to the sleep-promoting effects of various medications. We believe these experiments will lead to a better understanding of the molecular pathways controlling hypnotic responses. The study of such modifiers genes could also help to better understand sleep regulation in general and lead to the identification of new drug targets.

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Developing Novel Transgenic Zebrafish Tools for Studies of the Hypocretin/Orexin system

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Introduction: Hypocretins (orexins) are neuropeptides involved in the regulation of sleep and energy balance. This system is evolutionarily conserved, and is present in fish. In fish as in mammals, hypocretin neurons appear to project to all monoaminergic cell groups and appear to play a key role in the regulation of arousal. Loss of hypocretin (HCRT) transmission causes the sleep disorder narcolepsy in humans, canines and rodents. The zebrafish is a diurnal vertebrate, and is an excellent model organism for genome-wide mutagenesis and transgenesis. We have previously characterized the zebrafish and pufferfish hypocretin ligand and receptor genes. We have now used the hypocretin promoter to create transgenic zebrafish for use in the study of the development and function of the hypocretin system in the zebrafish.
Methods: For the initial construct, a 1.1 kb hypocretin promoter was isolated from the pufferfish tetraodon nigroviridis (tHCRT) and cloned in to the vector pEGFP-1. Three toxic transgene constructs were prepared based on this initial construct with the tHCRT promoter driving expression of full length and truncated mutant ataxin 3 (Q73) transgenes, as well as a mutant form of hypocretin from a human patient. In another set of experiments, a pufferfish histidine decarboxylase (HDC) gene promoter was isolated and cloned into the vector DsRed2-1. Prepared DNA was microinjected into 1 cell stage wildtype zebrafish embryos and transient expression was observed where possible by fluorescence microscope observation. All surviving larvae were raised to adulthood and intercrossed to identify founder animals through direct microscopic observation and PCR. Putative transgenic F1 animals were screened by direct observation or PCR of tail fin clips, and reared to create transgenic lines.
Results: Three tHCRT EGFP founders were identified. Transgenic F1 animals showed GFP fluorescence in hypocretin cells starting at 24 hours, and continuing to adulthood. Observed temporal and spatial GFP expression were consistent with in situ hybridization patterns detected in wildtype embryos with a zebrafish HCRT probe. One founder was obtained for the full-length ataxin 3 construct. PCR of individual F1 embryos indicated a low frequency of transgene transmission (<1/50 animals). One founder was identified for the human HCRT-mutant construct: in-frame fused GFP expression was observed in F1 progeny starting at 24 hours and was undetectable by 72 hours. Animals injected with truncated ataxin3-EFGP driven by tHCRT, and HDC-DsRed are currently being reared.
Conclusion: We have created several lines of transgenic zebrafish. In our experience this organism is ideally suited for transgenesis, and new lines may be created easily and rapidly. The use of fluorescent reporter genes in combination with naturally transparent zebrafish larve allows the study of live cells in the context of an intact live animal. These animals will be useful for the study of various neuronal projections, may serve as a basis for new genome-wide genetic screens, and possibly phenotypic rescue.

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Expression of temt in Basal Forebrain and Hypothalamus of Influenza-Infected Mice

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Introduction: After influenza infection, C57BL/6J mice develop increased slow-wave sleep (SWS) during the dark phase of the circadian cycle, whereas BALB/cByJ mice develop decreased SWS during the light phase. An analysis of CXB recombinant inbred mice revealed a quantitative trait locus (QTL) that was related to expression of the BALB/cByJ phenotype. This QTL, designated Srilp (sleep response to influenza, light phase) is located on Chr 6 in a 10-12 cM region between D6Mit74 and D6Mit188. Temt, which is located at region B3 of Chr 6, is a potential candidate for Srilp. The enzyme TEMT (thioether S-methyltransferase) catalyzes transfer of a methyl group from S-adenosylmethionine to sulfur, selenium or tellurium, yielding the corresponding methylonium compounds, and systemic administration of inorganic selenium compounds reduces sleep in rats. We report here that temt expression varies significantly as a function of mouse strain, brain region, and health status.
Methods: Adult male C57BL/6J and BALB/cByJ mice were inoculated intranasally at light onset under methoxyflurane anesthesia with uninfected allantoic fluid or with allantoic fluid that contained approximately 5×104 plaque-forming units of influenza strain A/HKX31. Mice were euthanized 30 hours after inoculation. This post-inoculation interval corresponds to a time at which BALB/cByJ mice show a "sleep fragmentation" phenotype, but C57BL/6J mice do not. Tissues from 5 mice were pooled for analysis, and the experiment was repeated 5 times. After euthanasia, viral titers were determined in lung tissue. Hypothalamus and basal forebrain were removed and stored in RNALater for subsequent extraction of total RNA. After digestion of total RNA with DNase I, cDNA was synthesized from total RNA, and primer pairs were designed for reverse transcriptase (RT) PCR. The PCR mix (10µl) consisted of 1?l of cDNA, 1µl of each 10pmol primer, reaction buffer, 200µM of each dNTPs, 2.5mM MgCl2 and 0.5U Taq polymerase (Promega). Reactions were carried out in a thermocycler with 5 minutes at 94°C, followed by 35 cycles of 1 min at 94°C, 1 min at 58°C, and 2 min at 72°C. PCR products were electrophoretically separated on agarose gel and visualized with ethidium bromide under UV illumination. Quantitative (real time) PCR (qPCR) was performed using a Smart Cycler Real-Time PCR instrument (Cepheid Inc.) and iQTM SYBR Green Supermix kit. The PCR mix (26.5µl) consisted of 1µl cDNA, 1µl with 10pmol of each primer, and 12.5µl of SYBP Green mix. qPCR was processed with 45 cycles of 30 sec at 62°C and 1 min at 72°C. Gene expression was quantified using Smart Cycler Software version 1.2f.
Results: QPCR revealed that expression of temt varied significantly as a function of mouse strain, brain region, and health status. Expression in hypothalamus was 546 ± 299 % higher in healthy BALB/cByJ mice as compared to healthy C57BL/6J mice ($n = 5$, $P = 0.029$), whereas expression in basal forebrain of healthy BALB/cByJ mice was only 14 ± 1% that of healthy C57BL/6J mice ($n = 5$, $p = 0.0001$). After influenza infection, expression of temt did not change significantly in either brain region of C57BL/6J mice. In contrast, infected BALB/cByJ mice showed reduced temt expression in both hypothalamus (5.46 ± 2.99 vs. 3.03 ± 0.93; $n = 5$; $p = 0.078$) and basal forebrain (0.14 ±0.08 vs. 0.026 ± 0.017 vs.; $n = 5$; $P < 0.024$) as compared to healthy BALB/cByJ mice. Similar relationships were also apparent using RT-PCR.
Conclusion: Healthy C57BL/6J and BALB/cByJ mice differ in temt expression in hypothalamus and basal forebrain. During influenza infection, BALB/cByJ mice show reduced expression in both brain regions, whereas C57BL/6J mice do not. These results imply that temt expression and/or TEMT activity may mediate strain-dependent sleep responses both under basal conditions and during microbial infections. Our data suggest the possibility that strain- and infection-related alterations in sleep may be influenced by temt and the metabolism of selenium.

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An Induced Mutation That Increases Active Sleep In Neonatal Mice Is Associated With Increased Wake Time In Adults

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Introduction: In a chemically (ENU) induced random mutagenesis screen we have identified a line of mice that shows increased amounts of active sleep (AS) as well as AS bout duration in neonatal animals. The altered AS phenotype appears to be due to a single gene mutation that is dominant or semi-dominant as evidenced by inheritance patterns in G2, G3 and G4 generations. We are now characterizing the sleep-wake patterns of adult animals showing the increase in AS duration as neonates.
Methods: The founder animal in this line (1GO598) was a male and was used to generate 32 G2 pups and the line has now been bred out to generation G4 by crossing back to C57BL/6J wild-type (WT) animals. Five of the G2/G3 male animals from this line that showed 75.4 - 86.9 % AS as pups (mean for data base = 55.33 ± 12.5%) were implanted with EEG/EMG electrodes as adults (3-4 months of age). All animals were maintained on an LD 14:10 cycle. Sleep was recorded for two baseline days 10-14 days after electrode placement. Adult sleep and wake characteristics in these animals were compared with our data base values for C57BL/6J WT animals.
Results: While wake time during the 14-hour light phase was similar between the 1GO598 line and WT mice (314 ± 8 vs 301 ± 5 min, $p = 0.2182$), the mice from the mutant AS line were awake significantly more during the 10-hour dark phase than WT animals (499 ± 14 vs 430 ± 10 min, $p = 0.0017$). Indeed, the total amount of wake time during the entire 24-hour period was increased by 81 minutes ($p = 0.0012$) whereas NREM sleep time was decreased by 77 minutes ($p = 0.0022$) in the mutant AS line. No other changes in the sleep-wake architecture have been evaluated at this time.
Conclusion: A mutation, which leads to an increase in neonatal AS time and AS bout duration is associated with an increase in total wake time of about 1.5 hours/24 hours in adult animals. All mutant animals are only carrying a single copy of the mutant allele, so the sleep-wake phenotype of neonatal and adult animals homozygous for the mutation is not presently known. The 1GO598 mutant line of animals should prove to be useful in not only mapping and identifying a gene that can affect AS time in neonates as well as wake time in adults, but also in developing a better understanding of the development of sleep, as well as the relationship between the behavior states of wake, AS, and quiet sleep in neonatal animals with the EEG defined sleep states of wake, REM and NREM sleep in adults.

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Expression of ghrhr and crhr2 in Basal Forebrain and Hypothalamus of Influenza-Infected Mice

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Introduction: The genes ghrhr (growth hormone releasing hormone receptor) and crhr2 (corticotrophin releasing hormone receptor 2) are located on mouse chromosome 6 within the genomic interval that defines the quantitative trait locus (QTL) Srilp (sleep response to influenza, light phase). Growth hormone releasing hormone (GHRH) promotes sleep in mice and other species, and mutant mice that lack functional ghrhr show reduced sleep after influenza infection. In contrast, corticotrophin-releasing hormone (CHR) promotes wakefulness. To determine whether ghrhr or crhr2 are likely to underlie Srilp, we assessed the expression of both genes in hypothalamus, basal forebrain, and pituitary of healthy and influenza infected C57BL/6J and BALB/cByJ mice using reverse transcriptase (RT) PCR and quantitative (real-time) PCR (qPCR).
Methods: Adult male C57BL/6J and BALB/cByJ mice were inoculated intranasally at light onset under methoxyflurane anesthesia with uninfected allantoic fluid or with allantoic fluid that contained approximately 5×104 plaque-forming units of influenza strain A/HKX31. Mice were euthanized 30 hours after inoculation. This post-inoculation interval corresponds to a time at which BALB/cByJ mice show a "sleep fragmentation" phenotype, but C57BL/6J mice do not. After euthanasia, lung was frozen for subsequent determination of viral titers. Hypothalamus, basal forebrain, and pituitary were removed and stored in RNALater for subsequent extraction of total RNA. After digesting total RNA with DNase I, cDNA was synthesized from total RNA, and primer pairs were designed for RT-PCR. The PCR mix (10µl) consisted of 1µl of cDNA, 1µl of each 10pmol primer, reaction buffer, 200µM of each dNTPs, 2.5mM MgCl2 and 0.5U Taq polymerase (Promega). Reactions were carried out in a thermocycler with 5 minutes at 94°C, followed by 35 cycles of 1 min at 94°C, 1 min at 58°C, and 2 min at 72°C. PCR products were electrophoretically separated on agarose gel and visualized with ethidium bromide under UV illumination. qPCR was performed using a Smart Cycler Real-Time PCR instrument (Cepheid Inc.) and iQTM SYBR Green Supermix kit. The PCR mix (26.5µl) consisted of 1µl cDNA, 1µl with 10pmol of each primer, and 12.5µl of SYBP Green mix. qPCR was processed with 45 cycles of 30 sec at 62°C and 1 min at 72°C. Gene expression and copy number were determined using Smart Cycler Software version 1.2f.
Results: RT-PCR revealed very weak expression of ghrhr in hypothalamus of healthy and infected C57BL/6J and BALB/cByJ mice and no expression in basal forebrain. In contrast, ghrhr was expressed strongly in pituitary of both strains. Expression of crhr2 increased in basal forebrain of infected vs. healthy BALB/cByJ mice, but an infection-related increase was not detected in C57BL/6J mice. QPCR data were consistent with RT-PCR findings. Hypothalamic expression of ghrhr was not influenced by health status, and expression was not detected in basal forebrain. Expression of crhr2 increased 1.4 fold in basal forebrain of influenza infected BALB/cByJ mice as compared to uninfected BALB/cByJ mice ($n = 5$, $P = 0.0057$), but did not change significantly in infected C57BL/6J mice. Hypothalamic expression of crhr2 did not vary in either strain as a function of health status.
Conclusion: Infection with influenza virus was associated with increased expression of crhr2 in basal forebrain of BALB/cByJ but not C57BL/6J mice. Because BALB/cByJ mice show fragmented and reduced sleep at the post-inoculation times associated with these data, and because CRH promotes wakefulness, our findings are consistent with a role for chrh2 mediating the sleep-modulatory effect of influenza infection in mice.

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Diurnal Variations In Bcl-2 Protein Expression In The Cerebral Cortex Of Rats

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Introduction: The neuronal excitability of several structures in the brain changes across the 24 hours. It seems that at least the neurons of the cerebral cortex are more active during the waking rather that sleeping period. Therefore, it is expected a structural or functional wearing. In consequence, a repairing process must take place. This repairing process may be a result of the activity of neurotrophic factors, i. e. Brain Derived Neurotrophic Factor (BDNF) and their intracellular cascades. A question we have about this process is which phase of the light-dark cycle favors better this repairing process. In order to approach this question we decided to study diurnal variations in molecules that regulate neuronal survival, i. e. Bcl-2 and Bax.
Methods: Diurnal variations Male Wistar rats (250-300 g) were maintained under a controlled dark-light cycle (12.12, lights on at 08:00 A. M.) with food and water ad libitum. A group of them were killed by decapitation at different hours: 9:00, 13:00, 17:00, 21:00, 1:00 and 05:00; all brains were rapidly dissected to isolate cerebral cortex, hippocampus and hypothalamus. Western blot Tissue samples were homogenized with proteases inhibitors and centrifuged in order to obtain a membrane enriched fraction. Proteins were quantified by using the Bradford technique and 60 ?g from each region were run in sodium dodecyl sulfate-polyacrilamide gel electrophoresis (SDS-PAGE) and transferred to PVDF membranes. Western blotting was performed using monoclonal antibody for Bcl-2(Santa Cruz Biotechnology). The statistical significance was obtained by using a two-way ANOVA test.
Results: Bcl-2 expression as assessed by Western blotting, exhibits diurnal variations in the cerebral cortex of the rat. The highest expression was detected in the dark rather than in the light phase of the cycle. Interestingly, no changes were detected in the hippocampus and in the hypothalamus.
Conclusion: On the bases of these findings, we believe that the dark phase of the cycle favors the neuronal survival.

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A Proteomic Analysis In Brain Following Sleep Deprivation Suggests A Generalized Decrease In Abundance For Many Proteins

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Introduction: The identification of differentially regulated proteins associated with sleep deprivation (SD) may provide insights into the biochemical mechanisms underlying sleep-wake physiology. Understanding these biochemical mechanisms may also lead to the development of novel drug therapies that modulate both sleep and wake-

fulness. In addition, changes in a number of different proteins may provide biomarkers that are diagnostic for underlying sleepiness or sleep disorders. As an initial step in this identification process we have utilized protein biochips with Surface-Enhanced-Laser-Desorption/Ionization Time-of-Flight Mass Spectrometry (SELDI-TOF-MS) detection to generate protein expression profiles from brain tissue extracts obtained from control and SD mice.

Methods: C57BL/6J mice were age and sex matched and divided into SD and control groups. In the primary experiment, 8 young adult males underwent 6-h SD and were compared to 8 control mice that were undisturbed in their home cage. Mice were kept on a 12:12 light:dark cycle, and SD began at light onset. At the end of the 6-h period, SD and control mice were sacrificed by cervical dislocation and brains rapidly removed. Cerebellum and brainstem were removed, and the remaining brain was dissected with a single mid-sagittal cut. The brain tissues were rapidly frozen on powdered dry ice and stored at -70C. Protein extracts were prepared by homogenizing the tissue in 9M urea buffer with protease inhibitors. After centrifugation, the supernatant was fractionated on a Q-HyperD anion exchange resin using a step-wise pH gradient of pH8, 5 and 3. All fractions were then profiled on weak cation exchange (WCX2), Cu2+-metal affinity (Cu2+-IMAC3), and hydrophobic (H50) ProteinChip Arrays.

Results: A series of proteins ranging from 5kDa to 20kDa were found to be differentially regulated ($P<0.001$) when comparing control vs. SD samples. While there were many changes in both directions, the nine most evident changes involved declines in protein following SD (representing about 2-fold to 5-fold lower levels), and in general declines outnumbered increases. One of the proteins was identified as cytochrome C oxidase, subunit Va (Cox5a), and this result was confirmed with a specific antibody.

Conclusion: A decrease in many proteins during SD suggests that a fundamental function of sleep may be to replenish proteins degraded during wakefulness. This may be especially true for small proteins, and proteins involved in energy metabolism, as studied here. It is also possible that the lower levels of many proteins simply reflect lower rates of synthesis during wake, which is consistent with previous 14C leucine autoradiographic studies. Given the generalized increase in many mRNAs during SD, it appears likely that some mRNAs are increasing while the respective protein is decreasing. For these mRNAs, the increase may allow for increased protein synthesis during sleep. In other cases, mRNA and protein may change in concert (with a typical lag for the protein) as appears to be the case for Cox5a (currently under study at the mRNA level). Time course studies of many mRNAs and proteins that change their abundance with time-spent-awake may help to address these questions.

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Genetic Evidence that Protein Kinase A Regulates Thalamocortical Oscillations during NREM Sleep

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Introduction: Computer models have suggested that activity during wakefulness could affect sleep and its associated oscillations via the cAMP/protein kinase A (PKA) pathway. PKA has been suggested to modulate thalamocortical synaptic plasticity during spindle oscillations during NREM sleep. Although several neurotransmitters that regulated sleep/wake states are known to increase levels of cAMP, the role of this signaling pathway in the regulation of sleep and its associated oscillations have not yet been characterized. To assess the role of PKA, we have characterized sleep/wake states using EEG/EMG recordings in R(AB) transgenic mice, which express a dominant negative form of the regulatory subunit of PKA in neurons within cortex, hippocampus, striatum and amygdala. These mice have reduced PKA activity in cortex and hippocampus, which results in the impairment of hippocampus-dependent long-term memory and long-lasting forms of hippocampal LTP.

Methods: Transgenic R(AB) and wild-type littermate mice were backcrossed in the hemizygous state to C57BL/6J for 11-13 generations, and bred in our colony under standard conditions. Adult mice (12-24 weeks of age) were implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes under isofluorane anesthesia. Mice were allowed two weeks recovery before recording. After baseline recording, R(AB) and wild-type mice were subjected to sleep deprivation using gentle handling.

Results: We have found that R(AB) transgenic mice exhibit normal amounts of NREM sleep and wakefulness, but exhibit 17 % more REM sleep per day than wild-type mice. R(AB) transgenic mice have more delta power (1-4Hz) during NREM sleep throughout the entire light-dark cycle, as well as less sigma power (10-14 Hz) during NREM sleep than wild-type mice. Sleep deprivation revealed that homeostatic regulation in R(AB) transgenic mice was comparable to wild-type mice, suggesting that an alteration in a mechanism unrelated to sleep homeostasis underlies the delta power phenotype. The sigma power rebound that lasted for many hours after sleep deprivation in wild-type mice was reduced in R(AB) transgenic mice. The decrease in sigma power in R(AB) transgenic mice is due to lower amplitude spindles. Differences in delta power and spindle oscillations could either be due to increased hyperpolarization of R(AB) cortical neurons or alterations in synaptic connections between cortical and thalamic regions. Our results suggest a role for PKA in sleep oscillations independent of homeostatic sleep or circadian regulation that may be responsible for modulation of delta spindle amplitude during NREM sleep.

Conclusion: PKA in a brain region outside of the medial pontine reticular formation activity can decrease REM sleep. Delta oscillations can be modulated by mechanisms independent of the sleep homeostat. A reduction PKA activity can result in the increased amplitude of delta oscillations reduced amplitude spindle oscillations.

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Altered Sleep Patterns in Mice Lacking the p50 Subunit of NF-Kappa B

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Introduction: Nuclear factor-kappa B (NF-kB) is a heterodimeric transcription factor that is implicated in sleep regulation. The p50/p65 heterodimer is a commonly expressed form of NF- kB in vivo. Increased activation of NF-kB occurs in rat brain during the circadian light phase (LP) and after sleep deprivation (SD). NF-kB modulates levels of the somnogens such as TNF-a and NO, which also show circadian variation. Both these substances play a role in regulation of slow wave sleep (SWS) and rapid eye movement sleep (REMS). However, whether NF-kB activation modulates sleep homeostasis or the circadian cycle has not been well established. To address this question, we characterized sleep in mice lacking the p50 subunit of NF-kB (p50-/-) and measured expression of TNF-a and nNOS.

Methods: p50-/- and control B6129PF2/J mice were surgically implanted with electrodes for recording EEG and EMG. After recovery from surgery, mice were housed in individual cages in sound attenuating

chambers on a 12:12 hour light-dark cycle at 21-220 C. We monitored sleep for 24h without disturbing the mice and for 42h after a 6-hour period of SD. nNOS protein in brain stem and serum TNF-a concentrations were assessed at light onset. Brain stem cytosolic protein (80ug) was resolved by SDS-PAGE, transferred to nitrocellulose membrane, and incubated overnight with specific primary polyclonal antibody. Membrane was incubated with HRP labeled goat anti-rabbit IgG secondary antibody, treated with Western blotting detection reagents, and exposed to Kodak XAR film. Serum TNF-a levels were measured by ELISA.

Results: Compared to the control strain (n =9), p50-/- mice (n =9) spent twice as much time in REMS during LP and showed a modest enhancement of SWS at 3h after light onset. The enhanced REMS was characterized by a greater number of REMS bouts (13.2+/-0.9% and 9.6+/-0.7% bouts per 2 hours for p50-/- and B6129PF2/J mice, respectively; $p<0.05$). In addition, p50-/- mice showed a greater rebound increase in REMS (4.6 +/-1.6%, 6 hr duration) and SWS (31.8+/-11.6%, 2 hr duration) after SD as compared to B6129PF2/J mice (REMS, 2.1+/-1.1%; SWS, 25.8+/-9.1%) ($p<0.05$ for both). nNOS protein in brain stem at light onset was markedly lower in the p50-/- compared to control mice (5.4 units and 9.0 units, respectively, normalized to actin; n=3 each). Serum TNF-a levels at light onset were higher in p50-/- (22.3 +/-2.0 pg/ml, n=5) than in B6129PF2/J mice (10.5 +/- 1.3 pg/ml, n=4).

Conclusion: p50-/- mice spent more time in REMS and SWS than B6129PF2/J mice both under baseline conditions and after 6h of SD. Brain stem nNOS protein levels were lower and serum TNF-a levels were higher in p50-/- mice, suggesting altered modulation of these somnogens in the absence of p50. These findings are consistent with a role for the normal p50/p65 heterodimer of NF-kB in the regulation of sleep.

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Pre-frontal Cortex Activation is Increased During an Auditory Paced Serial Addition Task (PASAT) in Moderate to Severe OSA: Preliminary fMRI Evidence

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Introduction: Obstructive Sleep Apnea (OSA) is associated with impaired performance on tests of cognitive executive functions (EFs), but the mechanisms leading to this impairment are unclear. We are examining the effects of OSA and hypoxia on regional cerebral blood flow patterns using functional magnetic resonance imaging (fMRI). We hypothesize that brain areas supporting the operation of EFs (e.g., dorsolateral prefrontal cortex (DLPFC), anterior cingulate gyrus) will demonstrate decreased levels of activation as measured by the blood oxygen level dependent (BOLD) signal during fMRI in OSA patients with hypoxia.
Methods: Subjects included men between the ages of 30-55, suspected of having OSA (Epworth Sleepiness Scale score ≥ 12, witnessed apneas during sleep, and habitual snoring). Subjects are excluded for contraindications to MRI, significant medical, neurological or psychiatric co-morbidities. Neuropsychological testing, MRI and the Beck Depression Inventory (BDI) were completed prior to diagnostic polysomnography (PSG). During MRI, subjects performed a Paced Auditory Serial Additional Test (PASAT) task that required them to indicate by button press, when they heard two successive numbers that added up to the number 10. On a subsequent day, PSG (split-or full-night) clinic evaluation was used to confirm the presence and severity of OSA. OSA with hypoxia was defined as minimum oxygen saturation level (MinO2) ≤ 89 and OSA without hypoxia as MinO2 ≥ 90. Our pilot data include 3 OSA patients with hypoxia (HYPOX) and 3 OSA patients (NOHYPOX) without hypoxia.
Results: Patients are currently 6 men with a mean age of 47.0 years. The HYPOX group (MinO2 = 88 ± 1.7 (mean ± SD), had an apnea hypopnea index (AHI) of 48.9 ± 40.9; sleep efficiency (SE) of 88.7 ± 6.1; and a 3% desaturation index (DI) of 29.0 ± 30.7. The NOHYPOX group (MinO2 = 95 ± 1.0) had an AHI of 29.6 ± 13.2; SE of 66.2 ± 6.1; a 3% DI of 3.2 ± 2.8. Scores on the BDI were similar between groups (HYPOX =13.3 ± 5.0; and NOHYPO = 12.3 ± 6.1). ESS scores at the time of cognitive testing were also similar (HYPOX =14 ± NOHYPOX = 14 ± 2.7). Both groups showed task-related activation ($p < 0.001$) in DLPFC and parietal regions consistent with previous findings in healthy subjects. The HYPOX group showed patterns of increased activation within DLPFC and increased overall activation, particularly over occipital cortex that was not observed in NOHYPOX group.
Conclusion: Our preliminary data suggest that during neurocognitive testing the BOLD signal within the posterior DLPFC of OSA subjects with hypoxia is increased, which is contrary to our working hypothesis. Increased patterns of activation may indicate a need for the recruitment of larger areas of DLPFC in order for OSA patients with untreated hypoxia to perform an EF task. Subject recruitment is on going and analysis of additional data will be necessary to substantiate these findings.

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Cerebellar Activity During an Alternate Tapping Task in Obstructive Sleep Apnea: Preliminary fMRI Evidence

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Introduction: The cerebellum is well known to support complex movement, coordination, and postural control and is especially sensitive to the effects of decreased oxygen metabolism. By use of blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) of the brain, we examined the effects of obstructive sleep apnea (OSA) in adult men with untreated OSA. We hypothesized that during fMRI of a coordinated bimanual motor task OSA patients with more severe hypoxia would demonstrate differing patterns of cerebellar activation, as compared to OSA patients with less severe hypoxia.
Methods: Subjects included men (N=6, mean age of 47 years) between the ages of 30-55 who were evaluated for OSA in a sleep disorders clinic. Subjects reported witnessed apneas during sleep and habitual snoring, and demonstrated an Epworth Sleepiness Scale (ESS) score ≥ 12. Subjects were excluded for contraindications to MRI, and significant medical, neurological or psychiatric co-morbidities. Subjects participated in an fMRI scan and neuropsychological testing before their diagnostic polysomnography (PSG) study. During MRI scanning, the subject performed an alternate (right and left hand) finger-tapping task in response to an auditory beeping signal. Blocks of 30 seconds of tapping alternate index fingers were followed by 30 seconds of resting while listening to the auditory beep. On a subsequent day, PSG (split-or full-night) clinic evaluation was used to confirm the presence and severity of OSA. OSA with hypoxia was defined as minimum oxygen saturation level (MinO2) ≤ 89 and OSA without hypoxia as MinO2 ≥ 90. Our pilot data include 3 OSA patients with hypoxia (HYPOX) and 3 OSA patients without hypoxia (NOHYPOX).
Results: The HYPOX group (n=3) had a mean MinO2 of 88 ± 1.7 (mean ± S.D.), apnea hypopnea index (AHI) of 48.9, ± 40.9, a 3% desaturation index (DI) of 29.0 ± 30.7, and a sleep efficiency (SE) of 66.2 ± 18.7, compared to the NOHYPOX group (n=3;MinO2= 95 ± 1.0; AHI = 29.6 ± 13.2; DI 3.2 ± 2.8; SE 88.7 ± 6.1). In comparison with the NOHYPOX group, the HYPOX group demonstrated generalized increased activation within the cerebellum, primarily in the lateral cerebellar hemispheres.
Conclusion: These preliminary results show a pattern of increased cerebellar activation during the performance of a coordinated bimanual task that may be associated with presence of OSA and severity of hypoxia in adult men. This increased level of activation may indicate that OSA subjects with hypoxia must recruit larger areas of the cerebellum in order to perform a coordinated bimanual task.

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Gender Comparison of Anterior-Posterior EEG Spectral Power During REM Sleep

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Introduction: Gender differences are reported in cognitive and psy-

chophysiological functioning, supporting differential use of anterior and posterior regions across genders. Indeed, women are thought to rely more on anterior areas for cognitive/motor tasks, whereas men rely more on posterior areas for the same tasks. It is not yet known whether this neurophysiological pattern also exists during sleep. We investigated this question in young adults during REM sleep, a state of spontaneous endogenous cortical activation.
Methods: Twenty-nine young right-handed healthy participants (15 women, age: 21.4 ± 1.7 years, range = 19 to 25; 14 men, age: 22.0 ± 2.0 years, range = 18 to 26) were recruited through public announcement. Exclusion criteria were a personal or familial (first degree) history of psychiatric or neurologic disorders, alcohol, medication, caffeine, extreme chronotypes, sleep disorders, and napping. Participants were asked to keep a regular sleep-wake schedule for two weeks before coming to the laboratory and filled an agenda during that period. Sleep was recorded for two consecutive nights. Night 1 served as an adaptation night and further screening of sleep disorders. Experimental data was collected during night 2 using a 13-electrode montage referred to linked ears. EEG amplitude power (μV/Hz) was determined with spectral analysis performed on 15 four-second artifact-free epochs sampled at 128 Hz during tonic REM sleep (without rapid ocular movements), equally distributed through the first three REM sleep periods. Frequency bands were Delta (0.75-3.75 Hz), Theta (4.00-7.75 Hz), Alpha1 (8.00-10.00 Hz), Alpha2 (10.25-12.75 Hz), Sigma (11.50-14.50 Hz) and Beta1 (13.00-19.75 Hz). Relative power (percent of total spectral power) was also computed. Values were grouped in four areas: Left Anterior (Fp1, F7), Left Posterior (P3, O1), Right Anterior (Fp2, F8) and Right Posterior (P4, O2). Comparisons were made for each hemisphere separately with 2 Genders × 2 Areas ANOVAS.
Results: We found a Gender × Area interaction in all absolute frequency bands, except for Alpha1. Post-hoc analyses showed higher power in Women than Men, and in Posterior areas than in Anterior areas. The amplitude of this difference between areas was higher in Women than in Men. Contrast between genders was greater in Posterior than in Anterior areas. Both hemispheres yielded similar results, except for Alpha1, which showed simple gender effect (higher power in Women) in the right hemisphere only. We found no gender or interaction effect for EEG relative power.
Conclusion: On one hand these results show a greater Anterior-Posterior contrast in Women than in Men. Only the non-circadian component of alpha activity (8-10Hz) was resistant to this interaction effect. On the other hand we failed to show a specific Anterior activation in Women and a specific Posterior activation in Men. REM sleep EEG thus only partly replicates Anterior-Posterior neuropsychological gender differences.

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Sleep Latency Testing as a Time Course Measure of State Arousal

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Introduction: The MSLT was developed to measure objective sleepiness. However, several recent studies have shown that the MSLT is also sensitive to changes in level of arousal associated with preceding activity, or exposure to bright light or music. Unfortunately, these previous studies primarily looked at sleep latency shortly after the arousing stimulus was presented. In the current study, repeated sleep latency tests were performed after a single activity manipulation to determine the time course response to that arousal as measured by several discrete sleep onsets.
Methods: Thirteen normal young adult Ss slept in the laboratory for two nights after adaptation. On the following mornings, the Ss had a baseline sleep latency test at 0900 followed by watching TV for 10 minutes (after one night) or a 5-minute walk (after the other night). They then had sleep latency tests at 0930, 1000, 1030, and 1100.
Results: Sleep latency did not differ on the nap prior to the experimental manipulation (latency 8.2 and 7.5 minutes respectively for the TV and Walk conditions). ANOVA for the nap latencies for the four post-manipulation naps showed a significant time by condition interaction ($F_{3,36} = 3.089$, $p = .039$). Pairwise comparisons showed that sleep latencies were longer following the walk in all naps except the third. Respective means were 5.3, 6.7, 7.9, and 8.6 minutes following TV and 13.5, 10, 10.6, and 12.8 minutes following the walk. Heart rate was significantly higher throughout all of the post-manipulation naps following the Walk as compared to the TV condition.
Conclusion: Sleep latency remains elevated for at least 100 minutes after the moderate arousal associated with walking for 5 minutes. This change is probably related to changes in underlying physiological arousal as measured in this study by heart rate, which also remained significantly elevated throughout the post-manipulation nap tests. These data indicate that 1) sleep latency can be used in a repeated fashion to measure changes in level of arousal and 2) relatively trivial amounts of state arousal associated with activity can influence nap latency for extended periods of time. Significant effort may be required to control for sources of arousal in MSLT evaluations. However, repeated sleep latency testing may be a valuable means to follow changes in level of arousal when prior amount of sleep is held constant.

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The Effects of Coping Strategies on Activity during Sleep Deprivation

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Introduction: Stressful events, for example total sleep deprivation (TSD), can be dealt with by the use of learned coping strategies. However, to date there has been little research done on coping strategies utilized by those who are sleep deprived. The relationship between coping strategies and habitual sleep length was examined in long sleepers (habitually sleep ≥9 hours per night) and short sleepers (habitually sleep ≤6 hours per night).
Methods: Coping strategies (measured by the Ways of Coping Questionnaire (WOC)) and activity during TSD (measured by actigraphy) were examined in 5 long sleepers (LS) and 5 short sleepers (SS) who underwent 36 hours TSD. The WOC is a 66-item questionnaire where subjects indicate the types of coping strategies used in a stressful situation. Each subject was assigned a relative score based on the frequency in which a particular coping strategy is used. The two coping strategies of interest were the problem-focused coping and emotion-focused coping. The actigraphy data was analyzed to record the mean activity and the variability in activity for each subject during TSD.
Results: On average, SS had greater mean activity levels and less variability in activity levels (i.e., more sustained activity) during TSD than LS. There was also an interaction between group (LS vs SS) and coping

strategies on activity levels. LS who reported relying more heavily on problem-focused coping strategies showed greater mean activity during TSD (Rsq=0.984, p=0.002) while SS showed no relationship between coping styles and mean activity. The SS had more sustained (less variable) activity during TSD when more emotion-focused coping strategies were used (Rsq=0.975, p=0.005).
Conclusion: To the extent that TSD is a stressful event, individuals could be expected to rely on their learned coping strategies to deal with a period of TSD. The fact that we found a relationship between coping strategies and activity levels during TSD in LS suggests that they were sufficiently stressed by the TSD to engage their learned coping strategies in order to offset that stress. Problem-focused coping is a type of active coping strategy, manifested here as mean activity levels during TSD. Thus, LS who typically use problem-focused coping showed more activity during TSD. The lack of a relationship between coping strategies and mean activity in SS suggests they were not as stressed by TSD or that we may have not measured the proper correlate of coping for this group. Also, the fact that SS are able to sustain their activity during TSD to a greater degree than LS further suggests that TSD may not be as stressing for SS. These findings may prove useful in an operational setting. First, they suggest that habitual sleep length may be useful in predicting who will find TSD stressful. Second, they suggest it may be possible to teach individuals to utilize previously learned coping strategies, or to learn new coping strategies, to bypass the potential stress resulting from TSD.

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Sleep Duration, Fatigue, And Work Performance Among Hospital Staff Nurses With Multiple Caregiving Roles

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Introduction: Irregular sleep/wake patterns, inadequate rest, and poor sleep hygiene occur frequently among family caregivers. Feelings of mental and physical fatigue often escalate when family caregivers are employed outside the home, and must manage multiple responsibilities. However, little attention has been given to understanding the effects on caregiver well-being when individuals combine family caregiving with professional caregiving. Therefore, this study a) compares fatigue among full-time hospital staff nurses who provide care for aging family members, children under 18 years of age, and those with no dependent care responsibilities; b) examines differences in sleep duration; and c) explores the effects on nurse work performance by caregiving status.
Methods: A random sample of hospital staff nurses (n = 392) recorded information about their sleep/wake patterns, work hours, level of alertness on duty, and errors daily in a logbook for 28 days. Participants also rated their daily fatigue levels. Of the 392 nurse participants, 391 identified their informal caregiving status as: 1) not caregiving (n = 197), 2) caring for children (n = 133), caring for elders (n = 32), or 3) caring for both children and elders (n = 29). Although 38.2% (n = 149) of the nurses were employed in 8-hour shift patterns, mean work hours ranged from 10.96 (no care dependents) to 11.54 (dual dependent care duties) hours per shift.
Results: The total amount of sleep obtained across all groups was 7.42 + 2.09 hours, with participants averaging fewer hours of sleep on work-days (6.77 hours) than non-work days (8.17 hours). On work days, mean total sleep durations for the four caregiving groups ranged from 6.43 hours to 6.83 (SD = 1.75) hours (no care dependents). Nurses who were providing elder care obtained the least amount of sleep, averaging 6.43 hours (SD + 1.74) of sleep on work days, with one quarter of the nurses in this group sleeping less than 5.75 hours/day. Nurses providing care to elderly relatives were also more than twice as likely to make an error at work (OR = 2.38; p = .005). However, elder care was only marginally associated with the prevalence of near misses (OR = 1.33; p = .33). No other associations between errors and near misses with caregiving status were apparent despite the fact that fatigue scores were significantly higher among nurses who were caring for both children and elders. Additionally, nurses providing concurrent elder and child care were also more fatigued than the caregiving other groups on non-work days. On average, this group of nurses worked more hours per shift than their other colleagues in the remaining caregiving groups.
Conclusion: Fatigue and inadequate sleep are issues for nurses in personal and professional caregiving roles. Nurses providing elder care at home obtained less sleep, were more fatigued even on non-work days, and likely to make errors at work. Fatigue levels among nurses providing concurrent elder and child care may be attributed to insufficient sleep combined with the burden associated with multiple caregiving responsibilities.

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Sleep Habits and Daytime Functioning in Students Attending Early versus Late Starting Middle Schools

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Introduction: Researchers have developed a clear understanding of adolescents' sleep requirements and demonstrated that middle and high school students do not obtain adequate sleep on weekday nights when schools start early in the morning (Carskadon & Acebo, 2002). Studies of high school students have concluded that students attending later starting schools report better academic performance and behavior and get more sleep due to later rise times on school mornings in comparison to early starting schools (Wahlstrom, 2001; Carskadon et al., 1998). This study examined sleep/wake patterns in students attending an early versus late starting middle school.
Methods: Two urban, New England, public middle schools were assessed. At the start of the 2002-2003 school year, School L delayed their start time from 7:15 am to 8:37 am while School E remained at 7:15 am. Students were assessed at two times of measure (fall and spring). 265 (School L = 128, School E = 134) 7th and 8th graders completed a survey in the fall and 205 in the spring (School L = 79, School E = 126). The 42-item survey included the Sleep Habits Questionnaire (revised, Wolfson & Carskadon, 1998), Adolescent Sleep Hygiene Scale (LeBourgeois et al., 2003), and self reported grades. The backgrounds of the students from the two schools were similar: 60% Caucasian, 19% Hispanic, 8% African American, and 13% other; 75 % of parents worked outside of the home.
Results: During the fall, students at School L reported waking up over 60 minutes later on school mornings (School L: M = 6:56am, SD = :58 vs. School E: M = 5:43am, SD = :39), obtaining 50 min. more sleep per night (School L: M = 534 min, SD = 77 vs. School E: M = 479 min, SD = 78), and departing for school almost 1.5 hours later than School E (p's

< .01). However, there were no school differences for sleep hygiene practices, school-night bedtimes, weekend sleep variables, self-reported sleep need, and sleep wake behavior problems. In the spring, School L students continued to sleep longer on school mornings due to later rise times and reported fewer sleep/wake behavior problems. In the fall, a school X sex effect was found for self-reported grades; School L females reported higher grades compared to those at School E. In the spring there was a school X grade effect for self-reported grades; 8th graders at School L reported higher grades than 8th graders at School E (p's < .01). Further analyses will look at teacher reported quarterly grades.
Conclusion: It is disconcerting that 28% of the students at both middle schools reported obtaining less than 7.5 hours of sleep on school nights. Students at the later starting school got significantly more sleep than students at the school with an early start time in the fall and spring. Similar to studies of high school start times, these findings demonstrate that middle schoolers' sleep patterns improve with a delayed school start time.

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Sleep Habits In Norwegian Adolescents In Spring And Late Fall
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Introduction: Norwegian adolescents report the highest morning sleepiness observed in 28 countries in cross national studies by the WHO on health and health related behaviour in young people. Boys report more morning sleepiness than girls in all age groups. Those data were collected in the beginning of December, and it is not known whether the reported behavior was influenced by season.
Methods: We have studied seasonal changes in behavior among high school students in Bergen (60.4 N), the second largest city of Norway. First year students from 3 high schools in the city center and 3 high schools close to the city were asked to take part in the study. In May and November/December 2002 294 students, 135 boys and 159 girls, 16.4 (0.6) [range 16-19] years old, participated. In November/December 2002 and May 2003 a second group of 526 students filled in the Karolinska Sleep Questionnaire, the Global seasonality score (GSS) questionnaire, Youth Self Report (YSR), a questionnaire on Subjective Health Complaints (SHC), Epworth Sleepiness Scale and Sleep for Science Morningness/Eveningness Questionnaire. Dependent t-tests were used to compare effect of season within group. Independent t-tests were used to compare data between boys and girls.
Results: So far preliminary analyses have been conducted on data from the first group of students, where 91.5% participated both in May and November/December. More students, particularly boys, reported more problems waking up in the morning in November/December than in May. Bedtime was later on weekend nights in November/December, and there was a trend towards later rise time on weekends. This was mostly due to the boys delaying bedtime and rise time on weekends in November/December. All students, the boys in particular, reported getting less sufficient sleep in November/December. Also, boys perceived their sleep of poorer quality in November/December as compared to May. Girls reported more problems falling asleep in May than boys. Both in May and November/December girls had more problems with nightly awakenings. Girls went earlier to bed both on school nights and weekend nights, and rose earlier on school days than boys in May as well as November/December. Also, girls rose earlier on weekends than boys in November/December. Girls perceived their sleep of poorer quality than boys in May.
Conclusion: Seasonality appears to have a significant impact on sleep in Norwegian adolescents. Boys in particular reported a negative effect on sleep parameters during November/December as compared to May. The high frequency of problems waking up in November/December in the whole group and particularly in the boys, agrees with the high frequency of morning tiredness as found in Norwegian adolescents by WHO. Our findings suggest that the WHO findings were related to the time of the year of survey administration (December).

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Objective Sleep Duration and Latency in a Population-Based Study of Middle-Aged Adults
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Introduction: Few population-based studies of sleep exist. Previous population-based studies have either collected self-reported characteristics of sleep, such as the National Sleep Foundation polls, or have focused on sleep disordered breathing, such as the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study. The aim of this study is to describe sleep duration and latency among middle-aged adults, using an objective measure of sleep in a population-based cohort study.
Methods: Actiwatches (Mini Mitter, Inc, Bend, OR) were distributed to 403 participants from the Chicago site of CARDIA (approximately 50% of the target population) between May and October 2003. CARDIA is an on-going prospective cohort study of the evolution of cardiovascular risk factors among adults aged 18-30 in 1985-1986. The original CARDIA cohort was balanced by sex, race, and education. Each participant wore the watch for three days, typically from Wednesday night to Saturday morning, and recorded bedtimes and wake times on a sleep log. Mean sleep duration is weighted by weekday and weekend nights. Sleep latency is estimated as the time from going to bed to falling asleep. Age-adjusted multivariable regression was used to examine the independent effects of race, sex, and education on sleep duration and latency.
Results: For the entire sample, mean sleep duration (±SD) is 6.15 h (±1.17 h), and mean sleep latency is 20.7 m (±26.6 m). Mean sleep duration by race-sex category is 5.16 h (±1.25 h) for African-American males, 5.92 h (±1.15 h) for African-American females, 6.07 (±1.09 h) for white males, and 6.82 h (±0.82 h) for white females. Mean sleep latency is 35.9 m (±44.1 m) for African-American males, 26.6 m (±25.1 m) for African-American females, 18.4 m (±24.4 m) for white males, and 12.9 m (±16.8 m) for white females. Mean sleep duration by education is 4.87 h (±1.83 h) for less than a high school degree, 5.83 h (±1.29 h) for a high school degree, 6.01 h (±1.08 h) for some college, and 6.42 h (±1.00 h) for a college degree or higher. Mean sleep latency is 50.6 m (±63.6 m) for less than a high school degree, 31.4 m (±29.8 m) for a high school degree, 25.3 m (±23.9 m) for some college, and 14.3 m (±19.1 m) for a college degree or higher. Adjusting for education and age, sex-race group is significantly associated with sleep duration, while only the difference between the lowest and highest education categories remains significant. Both race-sex groups and education are independently associated with sleep latency.
Conclusion: The results indicate strong race-sex differences in sleep duration and sleep latency. Education is also strongly associated with latency and weakly associated with duration after adjusting for race and sex. These data demonstrate that short sleep and poor quality sleep,

based on objective measures, may be more prevalent in African-Americans and individuals with lower education.

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Seasonal Changes In Self-Reported Sleep Duration In African-American and African Students Living in the Washington DC Metropolitan Area

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Introduction: From a biological standpoint, sleep duration is determined by an interaction between the circadian pacemaker and the sleep homeostat, and is related to the duration of biological night (Aeschbach et al 2003). The nocturnal duration of melatonin secretion, one marker of biological night, is longer in patients with seasonal affective disorder (SAD), but not in healthy controls, during winter relative to summer (Wehr et al. 2001). The purpose of the present study is to document changes in self-reported sleep duration across two seasons (i.e., the winter and summer months) in a large sample of African American and African college students in the Washington, DC metropolitan area. To our knowledge, this is the first study of seasonal changes in sleep in a non-Caucasian sample in the United States and the largest study to focus on seasonality in sleep duration in university and college students. We hypothesized that a) only students who met criteria for winter SAD or subsyndromal SAD (S-SAD) would report sleeping longer in winter than in summer, and b) seasonal differences in sleep duration would be greatest among African students, who report more problems with seasonal changes than African American students (Yousufi et al., in press).
Methods: African American and African college students from the greater Washington DC metropolitan area, DC (N = 575) completed a Seasonal Pattern Assessment Questionnaire (SPAQ), which was used to determine winter and summer sleep duration. Based on their responses, students were grouped into a winter SAD/S-SAD category or a no winter diagnosis category. We conducted a 2 (season) X 2 (sex) X (ethnicity) X 2 (winter diagnosis category) ANCOVA on sleep duration, controlling for age.
Results: The ANCOVA revealed a season X winter diagnosis interaction, Wilks lambda $F(1, 566) = 7.73$, $p = 0.006$. Students with winter SAD or S-SAD reported sleeping longer (by 21.0 minutes) in the summer than in the winter $t(77) = -2.15$, $p = 0.035$. In contrast, students with no winter diagnosis reported sleeping significantly longer (by 24.6 minutes) in the winter than in the summer, $t(496) = 6.57$, $p < 0.001$. There were no effects for ethnicity or gender on sleep duration.
Conclusion: Surprisingly, students with winter SAD or S-SAD reported sleeping shorter, rather than longer, in the winter. It is possible that students who experience winter seasonality increase their duration of wakefulness and sacrifice sleep in order to be able to meet higher academic demands (e.g., end of semester exams) in the winter when their energy, motivation and cognitive abilities are most impaired by their condition. It is also possible that in African and African American students winter depression has more typical (including insomnia) than atypical features (including hypersomnia). Additional studies with multiple ethnicities and parallel nonstudent samples are necessary to assess if these results are specific to college students and/or certain ethnic groups, and to explore the possible interaction between biological and social factors in determining sleep duration.

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Comparison of Self-Reported and Objectively-Measured Sleep Duration in a Population-Based Cohort Study

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Introduction: Subjective, self-reported measures of sleep are widely collected in surveys. However, the correlation between subjective and objective measures of sleep has not been well established. The purpose of this study is to examine the association between subjective and objective measures of sleep duration and sleep latency.
Methods: The data presented are from CARDIA, an on-going prospective cohort study of the evolution of cardiovascular risk factors among adults aged 18-30 in 1985-1986. Between May and October 2003, 403 participants (roughly 50% of the target participants in the Chicago center) completed sleep questionnaires, including the Pittsburgh Sleep Quality Index and the Berlin OSA questionnaire. Participants also wore an activity monitor (Actiwatch, Mini Mitter, Inc, Bend, OR) for three nights (typically from Wednesday night to Saturday morning) and kept sleep logs. Mean weekly sleep duration was weighted by weekday and weekend nights. Sleep latency is estimated as the time from going to bed to falling asleep. Participants are identified as at high risk of having sleep apnea based on responses to the Berlin questionnaire.
Results: For the full sample, the mean (±SD) difference between the objective and self-reported sleep duration is -0.72 h (±1.28 h), and the mean difference between the objective weighted sleep latency and subjective sleep latency is -0.13 h (±1.22 h). The Pearson's correlation between objective and subjective sleep duration is 0.37 ($p<0.001$), and between objective and subjective sleep latency, 0.36 ($p<0.001$). Correlations varied by race-sex group and by education. For sleep duration, the correlation was 0.03 ($p>0.05$) for African-American males, 0.53 ($p<0.001$) for white males, 0.14 ($p>0.05$) for African-American females, and 0.43 ($p<0.001$) for white females; between objective and subjective sleep latency, 0.13 ($p>0.05$), 0.32 ($p<0.001$), 0.36 ($p<0.001$), and 0.56 ($p<0.001$), respectively. The correlations between objective and subjective sleep duration by education categories are -0.31 ($p>0.05$) for less than a high school degree, 0.23 ($p>0.05$) for a high school degree, 0.34 ($p=0.001$) for some college, and 0.50 ($p<0.001$) for a college degree or higher. The correlations between objective and subjective sleep latency by education categories are 0.15 ($p>0.05$) for less than a high school degree, 0.29 ($p<0.05$) for a high school degree, 0.30 ($p<0.05$) for some college, and 0.41 ($p<0.001$) for a college degree or higher. Fifty-two (12.9%) participants are identified as at high risk of apnea, but apnea risk did not predict correlations between objective and subjective measures.
Conclusion: The results do not indicate a strong correlation between objectively measured sleep duration or latency and self-reported sleep duration or latency in this sample. In addition, the correlations vary greatly by race-sex category and education. Importantly for survey research, less education predicts lower correlation for both sleep duration and sleep latency. Further investigation is needed into the validity of self-reported sleep measures by race, gender, and socioeconomic status.

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Diurnal Preference, Depression, and Attachment Styles Among Older Adults

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Introduction: The Morningness-Eveningness Questionnaire (MEQ) is the most reliable scale to assess diurnal preference. It is highly correlated with circadian rhythm measures and with depression and personality characteristics. As we get older, there tends to be a shift in diurnal preference from evening-type to morning-type. Yet, it remains unclear whether diurnal preference might fluctuate throughout development or whether it develops in a manner analogous to attachment styles, which according to attachment theorists becomes stable and organized towards the end of the first year of life. If indeed a relationship could be established between attachment style and diurnal preference, this would offer an avenue whereby developmental nuances in diurnal preference among certain individuals can be studied further. The purpose of this study was to assess whether diurnal preference as defined in the MEQ is correlated with depression and attachment style in an older population.

Methods: Data for the present study came from a multifactorial study investigating the relationships between eye dysfunctions and circadian rhythms. The average age of the volunteers was 68.27 ± 5.97 years. A total of 70 volunteers were recruited, of which 65 provided valid data for the present analysis. This included self-rated measures of diurnal preference, depressed moods, and attachment; demographic and health data were also obtained. Diurnal preference was measured with the MEQ (α = 0.78). Depression was assessed with the Geriatric Depression Scale (GDS) (α = 0.79). Attachment was measured with the Relationship Style Questionnaire (RSQ), which categorizes responses in four groupings: secure (α = 0.54), preoccupied (α = 0.49), dismissing (α = 0.53), and fearful (α = 0.57).

Results: Classification of the MEQ scores was: ET = 3%, NT = 35%, and MT = 62%, and the distribution was normal (mean = 60.76 ± 9.01, and skewness = -0.45). A greater degree of skewness was noted for GDS (mean = 7.80 ± 4.74, and skewness = 0.98) and RSQ (mean = 76.65 ± 15.71, and skewness = 0.96). To examine relationships of diurnal preference to attachment style and depression, partial correlations were used controlling for ethnicity, age, sex, BMI, education, and income. Results showed that the MEQ is significantly correlated with depression (r_p= -0.49, $p < 0.05$). Although statistically significant results were not found for attachment styles, important trends suggested that the MEQ is associated with the secure (r_p= -0.31, NS) and dismissive (r_p= 0.31, NS) attachment dimensions. A power test suggested that for a sample size of 80, we would have had adequate power (82.1%) to detect statistically significant results.

Conclusion: As expected individuals scoring high on the MEQ (i.e., MT) reported significantly less depressed moods. The hypothesis that attachment styles are related to diurnal preferences was not supported by the present findings. However, important trends suggested a relationship of diurnal preferences to the secure and dismissive attachment dimensions. These correlations are expected to reach statistical significance in a larger sample. Future studies might also consider examining these relationships in a younger sample.

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Prevalence Of Insomnia And Depression Among Older Russians Living In Brooklyn, NY

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Introduction: The ECA study estimated that 27% of American adults ages 60 and above exhibited subsyndromal depression. In the same age group, estimated incident insomnia, which is intricately connected with depression, ranges from 23% to 34% according to the EPESE. Specifically, rates of sleep complaints among older adults in East Boston were as follows: difficulty falling asleep (DIS), 17%, difficulty maintaining sleep (DMS), 33%, and early morning awakenings (EMA), 17%. To our knowledge, prevalence estimates of sleep complaints for older Russians living in the US have not been reported, but there are suggestions that the prevalence of depression in this ethnic group may be higher than that for the general population. This study addresses relationships between self-reported depressed mood and insomnia in a community-based sample of older Russians.

Methods: Volunteers (n = 307) in this study were urban community-residing older Russians (ages: 50-95 years, mean = 72.64 ± 9.62; women = 54% and men = 46%). Surveys were conducted in a semi-structured environment as part of a study assessing health-care needs, beliefs, and attitudes. Bilingual educators administered surveys in various community centers, enlisting representative Russian aggregates. Surveys were available in English and Russian. Measures for the analysis included demographic and health-related data. Respondents providing valid data received $20 for their participation. Data were coded and entered in SPSS 10.0 for analysis.

Results: Eighty-two percent spoke Russian as their primary language, 13% English, and the remaining 5% spoke either Yiddish or Georgian. Eighty-nine percent of the volunteers had at least a High School degree; 27% were married and 73% were single, divorced, or separated. Forty-one percent lived alone, whereas 59% lived either with a spouse, their children, a family member, or a friend. Overall, 93% reported at least one of several major health problems: hearing (26%), vision (48%), breathing (13%), hypertension (53%), snoring (28%), diabetes (26%), arthritis (53%), cancer (11%), and weight (34%). Forty-five percent reported DIS, 42% DMS, 25% EMA; 25% indicated daytime sleepiness (DS). Forty-three percent considered depression to be a major impairment, and 53% knew someone living with depression. Sixty-three percent indicated that they were moderately to extremely depressed or anxious at the time of the survey. Using Fisher's Exact test, we found significantly greater rates of sleep complaints among depressed volunteers (DIS: 39% vs. 61%, $\chi 2 = 33$, $p < 0.0001$; DMS: 34% vs. 66%, $\chi 2 = 45$, $p < 0.0001$; EMA: 36% vs. 64%, $\chi 2 = 18$, $p < 0.0001$; DS: 41% vs. 59%, $\chi 2 = 10$, $p < 0.001$).

Conclusion: Older Russians in Brooklyn may be characterized by a greater rate of depression and insomnia than the general US population. As expected, volunteers reporting depressed moods were also likely to report insomnia. While the present data do not allow a definitive explanation of the reasons why such a large number of older Russians reported being depressed and having trouble sleeping, one could argue that social isolation and language barriers may play an important role.

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Sleepiness and it's Correlates in a Norwegian Population

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Introduction: Pathological sleepiness can be defined as marked susceptibility to falling asleep in situations that are commonly not soporific. The most common trait measure of sleepiness is the Epworth Sleepiness Scale (ESS). The ESS has been used widely in clinical studies, but few studies have investigated the prevalence of pathological sleepiness in the general population. We therefore conducted an epidemiological study of sleepiness and it's correlates in the general adult population.
Methods: 2301 respondents (45.3% males/54.7% females) participated in a telephone interview conducted by an opinion-research institute, employing the next birthday technique. Mean unweighted age of the sample was 47.6 years (SD = 15.7; range 17-90 years). In all, 1301 interviews were conducted in December 2002/January 2003, whereas 1000 interviews were conducted in June 2003. The respondents answered questions related to demography (age, gender, socioeconomic status, and body mass index; BMI) and sleep related variables (night work, insomnia, cataplexy, restless legs, limb movements in sleep, loud snoring, breathing pauses in sleep and depression). They also completed the ESS. Age was dichotomized into 54 years and below or 55 years and older. Socioeconomic status was dichotomized into below or above mean (based on household income and education), and body mass index was dichotomized into BMI < 30 or BMI ≥ 30. The sleep related variables were dichotomized into symptom not present (based on the response alternative 'never') or present (based on the response alternatives 'sometimes', 'usually' or 'always'). Pathological sleepiness was defined by an ESS score of 11 or above. In order to investigate correlates to pathological sleepiness, logistic regression analyses were conducted where sleepiness constituted the criterion variable and where the demographic and sleep related variables constituted the predictor variables.
Results: The mean score of ESS in the general population of Norway was 6.91 (SD = 3.78). In all, 17.7% of the population had a score on ESS that was higher than 10. Based on an univariate logistic regression analysis it was shown that neither season, age, socioeconomic status, BMI or insomnia were significantly related to pathological sleepiness. However, male gender (OR = 1.42, 95%CI = 1.12-1.81), night work (OR = 1.45, 95%CI = 1.08-1.95), cataplexy (OR = 2.18, 95%CI = 1.57-3.02), restless legs (OR = 1.39, 95%CI = 1.08-1.78), limb movements in sleep (OR = 1.76, 95%CI = 1.31-2.38), loud snoring (OR = 1.38, 95%CI = 1.07-1.77), breathing pauses in sleep (OR = 1.84, 95%CI = 1.20-2.80), and depression (OR = 1.56, 95%CI = 1.22-2.00) were significantly related to pathological sleepiness. When all these eight variables were included in a multivariate logistic regression analysis only three of them maintained a significant relationship with pathological sleepiness; male gender (OR = 1.37, 95%CI = 1.02-1.85), cataplexy (OR = 1.80, 95%CI = 1.19-2.73), and depression (OR = 1.60, 95%CI = 1.18-2.17).
Conclusion: The overall prevalence of pathological sleepiness in the Norwegian adult population was high. Male gender, cataplexy and depression constitute significant correlates to pathological sleepiness in this study.

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Differential Effects of Cage Change and Novel Object on Sleep in BALB/cJ (C) and C57BL/6J (B6) Mice

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Introduction: Routine cage change (CC) and novel objects (NO) presented in the home cage are increasingly being used as experimental manipulations to examine alterations in sleep, especially those that may be related to anxiety. C mice have been suggested to have trait anxiety and, compared to B6 mice, have greater anxiety-like behaviors in novel environments. In this study, we examined the effects of CC and NO on sleep and the relationship between sleep and anxiety-like traits of C and B6 mice.
Methods: C (n=7) and B6 (n=8) mice were used in the study. The mice were implanted for recording EEG and activity via telemetry and allowed to recover from surgery. In the CC condition, the mice were placed into a clean cage with fresh bedding and, for control, they were removed from and placed back into the same cage. In the NO condition, a 1.25" PVC Tee was placed in the cage and, for control, the cage was opened without placing the Tee. The manipulations occurred at one-week intervals and sleep was recorded for 22 h after each condition. Wakefulness, rapid eye movement sleep (REM) and non-REM (NREM) were visually scored in 10 sec epochs. Data for the light period were analyzed in two 5-h segments (blocks 1-2) and for the dark period in two 6-h segments (blocks 3-4). Comparisons were conducted with Tukey tests. Values presented are Mean±SEM in min.
Results: After CC and NO, C and B6 mice showed significant increases in the latency to NREM and REM compared to controls. NREM latencies were longer after CC (C: 190±28; B6: 139±9.6) than after NO (C: 78±7; B6: 76±10). Following both handling controls, C mice displayed longer NREM latencies than B6 mice. After CC, both C and B6 mice displayed reduced NREM, REM and total sleep during block 1, and C mice also showed reduced REM during block 2. The reduction of total sleep in block 1 was greater in C mice (control: 185±4.9; CC: 75±18) than in B6 mice (control: 200±6.3; CC: 124.7±5.9). There were no significant changes in overall sleep amounts after NO in either strain. Spectral power analyses found significantly higher density in the 0.5-4 Hz frequency band during NREM with both CC and NO in C mice, but not in B6 mice.
Conclusion: CC and NO produced increased sleep latency, but only CC reduced total sleep in both strains in the block analysis. The more anxious C mice showed greater sleep loss than did B6 mice, and C mice also showed longer sleep latencies in the control conditions. Interestingly, sleep alterations in mice after CC and NO show several parallels to the first night effect in humans. These include prolonged sleep latency and reduced total sleep as seen in normals and patients with anxiety, amount of sleep change related to amount of change in recording environment, and greater sleep loss as seen in patients with anxiety. C mice may also show greater sleep loss across environments that could produce a "ceiling effect" in certain situations.

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Rat Strain Differences in Sleep Architecture after Experiencing Environmental Novelty and Short Duration Involuntary Sleep Loss

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Introduction: Genetic and physiological diversity amongst rodent strains provide the potential for developing models that may give insight into the factors that regulate sleep in response to environmental challenges. We examined baseline sleep in two inbred (Lewis (LEW); Fischer 344 (F344)) strains and one outbred (Wistar (WST)) strain that vary on a number of behavioral, neuroendocrine and physiological variables. We then examined sleep after manipulations (cage change (CC) and open field (OF)) that putatively would produce short-term internally generated alterations in sleep by presenting the animals with novel stimuli and after short-term forced wakefulness (FW) in the home cage.
Methods: LEW (n=8), F344 (n=8) and WST (n=7) rats (90-day-old males) were implanted with electrodes for recording EEG and EMG. After recovery from surgery, baseline sleep was recorded for 48 h and compared across strains. Afterwards, sleep was recorded following CC, after 1 h in OF and after 1 and 4 h of FW (touch or handling used to prevent sleep onset). Recordings were separated by at least 7 days, and scheduled such that sleep was recorded for 20 time-matched h after each treatment. The data were analyzed for 8 h light and 12 h dark period totals. Comparisons were conducted with Tukey tests ($p < 0.05$). Values presented are in min (means ± SEM).
Results: Strain rankings of baseline total 24 h NREM were LEW (693±47) > WST (566±39) = F344 (521±9), and for total 24 h REM were LEW (103.6±6.3) > F344 (84.1±4.3) and WST (94.5 ± 5.1) = LEW and F344. WST showed significantly increased NREM and REM during the dark period after OF, but no significant alterations in sleep after CC in any of the analyses. WST also showed increased NREM and REM during the light and dark periods after 1 and 4 h FW. F344 showed significantly increased NREM during the light period in all treatment conditions, and increased REM in the light period after all treatments except CC. However, F344 showed no significant alterations in dark period sleep. LEW had no significant alterations in NREM after any of the behavioral treatments. Significant increases in REM were observed in the dark period after OF, and in the light and dark periods after 4 h FW.
Conclusion: Following previous reports (Opp, M.R. Physiol Behav. 1997 63: 67-74), LEW rats exhibited greater baseline sleep than F344. LEW rats also showed the least alterations in NREM after all behavioral treatments. The results suggest within strain similarities between sleep alterations spontaneously arising in response to novel environmental stimuli and those occurring after involuntary short-term sleep loss. Examining genetic and neural differences between these strains could provide insight into the factors responsible for specific alterations in sleep in response to environmental challenges.

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The Effect of Restraint Stress on Sleep in Mice: Strain Comparison

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Introduction: Restraint is a commonly used physical stressor that when applied in the light period produces an initial decrease in sleep and subsequent increase in dark period sleep. We previously found that fear-conditioned emotional stressors (cues and contexts) produce alterations in sleep that vary with the relative amount of anxiety-like behaviors exhibited amongst mouse strains. In this study, we examined the effect of restraint on sleep in three of those strains (BALB/cJ (C), C57BL/6J (B6) and DBA/2J (D2)) to determine whether responses to restraint also varied with strain.
Methods: D2 (n=10), B6 (n=4) and C (n=4) mice were obtained from Jackson Laboratories. The mice were surgically implanted with transmitters for recording EEG and activity via telemetry. Following 48 h non-interrupted baseline sleep recording, the mice were restrained in their home cages for one hour during the 4th h after lights on by placing them in a plastic tube (2.5 X 2.5 X 8.0 cm) that allowed restricted movements of the fore- and hindlimbs. Afterwards, they were released from the tube and sleep was recorded for the following 20 h. Wakefulness, NREM and REM were visually scored in 10 sec epochs based on EEG and activity. Sleep was calculated as percentage change relative to baseline ((treatment - baseline) / baseline *100) in the 8-h light and 12-h dark periods and comparisons were conducted with paired t-tests (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).
Results: After restraint, D2 mice exhibited significant reductions in light period total sleep (-16.5±4.3%**), NREM (-15.9±4.2%**) and REM (-27.0±8.6%**), and significant increases in dark period total sleep (69.3±11.7%***), NREM (64.2±11.6%***) and REM (163±42.5%***). In B6 mice, reductions in light period sleep did not reach significance, but there were significant increases in dark period total sleep (29.6±3.7%**), NREM (25.4±4.3%**) and REM (111±37.8%*). In C mice, decreases in light period total REM (-67.4±11.5%**), and increases in dark period total sleep (45.9±10.5%*) and NREM (45.5±9.6%*) reached significance.
Conclusion: Restraint produced similar patterns of sleep (immediate decrease and subsequent nocturnal increase) in all three strains, though significance was not always reached in the preliminary analysis in B6 and C mice when the entire light or dark recording periods were considered. There were also strain differences in the durations of periods in which significant decreases and increases in sleep were observed; however, these did not follow a simple relationship to the relative level of anxiety between strains. Sleep alterations after restraint differ considerably from those seen after fear-conditioned stimuli. Light period restraint produces initial reductions in both NREM and REM whereas fear conditioning typically has a greater impact on REM. In addition, we have not observed rebound sleep after fear conditioning in any of the mouse strains we have studied thus far.

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Investigating the Relationship between Subjective Assessment of Sleep and Mood

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Introduction: Alterations in subjective assessments of sleep quality and quantity have been associated with changes in mood, with decreased sleep quality typically associated with increased mood disturbance. This relationship is thought to be present particularly in individuals suffering from insomnia, but has not been examined widely in normal sleepers. Typically this relationship is examined via alterations in sleep duration and not manipulations of mood. The aim of the current analysis was to examine the relationship between subjective assessments of sleep and mood in a population of healthy subjects undergoing a stress induction protocol.

Methods: Sixty healthy subjects (29m; 31f; aged 22-45y) who reported no problems with their sleep completed a single-day in-laboratory protocol. Subjects completed a range of psychometric and sleep questionnaires, including the Pittsburgh Sleep Quality Index (PSQI) and self reported sleep duration on the previous night. During the testing session subjects completed neurobehavioral assessment batteries (NAB) that involved both low stressor and high stressor components. Stress levels were altered by varying task difficulty, task duration and feedback provided to the subjects via the computer and experimenter. Following completion of each component of the test batteries, subjective ratings of mood were assessed using the Profile of Mood States (POMS). Relationships between sleep duration, PSQI variables and mood variables were analyzed using Pearson's correlations.
Results: We expected that subjects who reported sleeping poorly at home would have greater mood disturbance when provoked by a stressful situation. Poor sleep, as reflected by the PSQI global scale, was correlated with POMS total mood disturbance following both the low stressor ($r=0.414$, $p=0.003$) and high stressor ($r=0.348$, $p=0.006$) test batteries. There was a significant correlation between POMS vigor and both self reported sleep duration ($r=0.401$, $p<0.001$) and PSQI sleep quality ($r=0.509$, $p<0.001$) following the high stressor test battery, such that increased levels of vigor were associated with increased sleep duration and better sleep quality. In addition, longer self-reported sleep latencies were correlated with POMS measures of increased depression-dejection ($r=0.576$, $p<0.001$), increased anger-hostility ($r=0.507$, $p<0.001$), increased fatigue ($r=0.446$, $p<0.001$), increased confusion-bewilderment ($r=0.461$, $p<0.001$), and increased total mood disturbance ($r=0.396$, $p=0.002$).
Conclusion: These findings illustrate that the relationship between decreased sleep quality and decreased mood previously described in insomniacs, is also present in healthy individuals with no evidence of any sleep disorder. Further, expression of this relationship is amplified following exposure to stressful stimuli.

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Peppermint Odor Modifies Subsequent Sleep and Sleepiness in Young Men and Women

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Introduction: We previously found that pre-bedtime exposure to lavender, a mild soporific, significantly increased slow-wave sleep and differentially modified WASO latency, stage 2 and REM sleep in young men and women. By contrast, little is known about whether an arousing olfactory stimulus affects subsequent nighttime sleep. Previous studies show that peppermint enhances alertness in sustained attention tasks and increases stage 1 sleep when presented during napping. Therefore, this study investigated the effects of an alerting olfactory stimulus presented before bedtime on subsequent polysomnographic and subjective sleep and sleepiness. In addition, since women consistently show better olfactory abilities than men, we investigated gender differences in such effects.
Methods: Subjects were 10 women and 8 men, ages 18-26 (mean age ±SD, 20.2 ±2.2 y), in good physical and psychological health without sleep disturbance. Smoking, oral contraceptive or CNS medication usage, or extreme morningness/eveningness were exclusionary. Subjects completed three consecutive overnight sessions: one adaptation, one stimulus and one control night (stimulus/control night order was counterbalanced). Subjects received an intermittent presentation (first four minutes of each ten-minute period) of peppermint essential oil or a control (distilled water) from 2310h-2340h. Subjects rated the pleasantness, intensity and quality of peppermint or water using Likert scales at 2314h and 2344h. Karolinska Sleepiness Scale (KSS) and Stanford Sleepiness Scale (SSS) measured self-rated sleepiness at 2355h and 0815h, while subjective sleep measures were assessed at 0815h. Sleep was polysomnographically recorded from 0000h-0800h. Records were scored in 30-second epochs using Rechtschaffen and Kales' standard scoring criteria. Repeated measures analyses of variance, with gender as a between-subjects factor, examined differences in all measures between the control and stimulus sessions.
Results: There was a significant condition x gender interaction for NREM duration. Women showed a longer NREM duration in the stimulus than control session, while men showed a shorter duration. Peppermint increased stage 1 %SPT and stage 2 and stage 4 latencies compared to water, showing small to medium effect sizes, but only trends toward statistical significance. Although subjective sleep assessments did not differ significantly between sessions, morning SSS scores showed a significant condition x gender interaction. Men, but not women, felt significantly sleepier upon awakening following the stimulus than control session. There were no significant overall gender differences in objective or subjective sleep. Furthermore, peppermint was rated as significantly more pleasant, intense and elating than water, with larger differences in women than men for the latter two measures.
Conclusion: Peppermint presentation before bedtime differentially affects NREM duration in men and women. Overall, women showed longer NREM duration with peppermint while men showed a shorter duration. By contrast, men, but not women, were sleepier upon awakening following evening peppermint exposure, perhaps as a result of less NREM sleep. Furthermore, since peppermint was rated as more pleasant, intense and elating than water, with larger differences in women, these measures may relate to the gender-differentiated effects. Nighttime peppermint presentation may serve as a nonphotic method for producing significant effects on sleep and sleepiness in young men and women.

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Explaining the Differences in Residency Training Experiences: The Combination of Weekly Work and Sleep Hours Predicts More than Either One Alone

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Introduction: Introduction: Although reported weekly work and sleep hours during residency training are significantly correlated ($r = -.39$), this relationship is less robust that generally assumed. This suggests that they may function independently in predicting residency training experiences.
Methods: Methods: Using the American Medical Associations Graduate Medical Education database, a national, multi-specialty, random sample of PGY1 and PGY2 residents in the 1998-1999 training year was surveyed by mail. Residents completed a 5-page survey requiring 144 separate responses about their residency experience. Completed surveys were received from 3,604 of 5,616 residents contacted, a 64.2% response rate. Residents across all specialties averaged 79.4 (std.=19.2) hours of work per week and 41.1 (std.=6.6) hours of sleep per week (5.9 hours/night). The combined effects of reported work and sleep hours were assessed by dividing residents into four groups, those reporting: 1) 80 work hours or less per week and more than the average amount of sleep time (LW/MS, n=1,247); 2) 80 work hours or less per week and less than the average amount of sleep time (LW/LS, n=774); 3) more than 80 work hours per week and more than the average amount of sleep time(MW/MS, n=489); 4) more than 80 work hours per week and less than the average amount of sleep time (MW/LS, n=959). The magnitude

of the relationship of weekly work and sleep hours with a variety of variables was also estimated by use of multiple regression.
Results: Results: Analyses by 2 x 2 ANOVA using Type III sum of squares showed a consistent pattern in which the combined main effects of work and sleep time explained more of the variance across a wide variety of variables including: satisfaction with learning, satisfaction with residency experience, perceived stress, working without adequate supervision, learning from attending physicians, conflict with professional colleagues, significant weight change, serious accident or injury, alcohol use, reports of medical errors, working while impaired, and observations of others falsifying medical records, mistreating patients, or working while impaired. Importantly, only main effects, but no interaction terms were statistically significant. Overall, residents in the LW/MS group reported the most favorable residency experiences, while residents in the MW/LS group reported the least favorable experiences. The experiences of the LW/LS and the MW/MS groups were approximately the same. Regression analysis showed that for each additional average weekly sleep hour, .65% fewer respondents reported having made a medical error; for each additional weekly work hour, .19% more respondents reported having made a medical error.
Conclusion: Conclusions: Work hours and sleep hours function independently in shaping residency training experiences. The combination of both factors gives a clearer prediction of residents learning, health, patient safety, and professional conduct than either one alone. Our data suggest that long work hours can be offset by increased sleep time, or that shorter work hours are needed to compensate for inadequate sleep time. It seems unlikely that the recent 80 hour workweek standard will resolve current resident and patient safety concerns unless the essential sleep needs of residents are also addressed.

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A Comparison Of Neurobehavioral Performance In Pediatric Residents Following Heavy Call And Alcohol

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Introduction: Although heavy call and related sleep loss negatively affects residents' well-being and professional performance, no study has assessed resident performance under real-life conditions against an accepted criterion of functional impairment, such as a moderately elevated blood alcohol concentration. We examined performance on a neurobehavioral test battery and ability to self-monitor performance comparing four conditions: rested (Light Call; LC), sleep loss (Heavy Call; HC), Rested + Alcohol (LC/Alcohol), and Sleep Loss + Placebo (HC/Placebo).
Methods: Thirty-four residents (mean age 28.7 years (sd 2.7), 18 women) from the Brown University Pediatric Residency program (14 PL-1, 15 PL-2, 5 PL-3) were tested twice beginning at 1500 hours: after a month of light call (LC and LC/Alcohol) and post-call after a heavy-call (q 4 or q 5) month (HC and HC/Placebo). Sleep was monitored by actigraphy and sleep diary for the week before each session. Tests included the 10-minute Psychomotor Vigilance Task (PVT) and a 30-minute simulated driving task. The alcohol beverage-vodka (.6 g/kg for men, .55 g/kg for women) mixed with tonic water in a 1:5 ratio-was consumed after completing the first neurobehavioral battery in the LC condition; the same quantity of the placebo beverage-three drops of vodka floated on tonic water-was similarly administered in the HC condition. Participants rated their performance after each neurobehavioral task on a 1 (extremely good) to 7 (extremely poor) scale. PVT variables were median reaction time and number of lapses. Driving variables were lane position variability, speed variability, and off-road incidents.
Results: Mean breath alcohol concentrations for the LC/Alcohol condition taken before and after each task were .043 g% (sd .01) for PVT and .038 g% (sd .009) for simulated driving. For most variables, performance was worse in the two HC conditions and the LC/Alcohol condition compared to LC alone (e.g., median PVT reaction time [$F(3,78)=9.02$, $p<.001$]; simulated driving lane position variability [$F(3,99)=12.08$, $p<.001$]). Number of PVT lapses in the LC/Alcohol condition, however, did not differ significantly from LC without alcohol. Driving simulator speed variability and off-road occurrences were greater in the HC conditions compared to LC/Alcohol ($p<.05$). Men manifested more off-road events than women, but no other sex differences nor main effects of residency year on performance were found. Post-test performance ratings were significantly correlated with actual performance for both tasks, ranging from $r=0.37$ for the LC condition on the PVT to $r=0.69$ for the HC condition on the driving simulator; the one exception was that ratings in the LC/Alcohol condition were not significantly related to actual simulated driving performance.
Conclusion: Residents performed as poorly or worse after a month of heavy call than with moderate alcohol intoxication on a light-call month, and both were worse than "basal" performance during light call. Awareness of post-call impairment, however, may be greater than with alcohol. These findings have important implications for resident safety and for training programs in light of the recent change to ACGME regulations concerning resident work hours.

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The Effect Of Work Breaks On Performance

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Introduction: Research has shown that short breaks can improve performance and decrease subjective fatigue during sleep deprivation and other laboratory protocols. Since recent studies have shown that hospital staff nurses frequently work long hours, the goal of this sub-study is to determine if nurses who were able to take a break during their shift would report fewer difficulties remaining alert and make fewer errors than those who were not able to take a break during their shift.
Methods: Three hundred and ninety-three randomly selected nurses participated in a larger study of staff nurse fatigue and patient safety. Data collected for 28 consecutive days included information about participants' sleep, scheduled and actual work hours, errors, episodes of drowsiness and actual sleep on duty, and difficulties driving home due to drowsiness. Participants were also asked if there were able to take a break or sit down for a meal during their shift, to indicate the duration of their breaks and meal period, and if they were relieved of patient care responsibilities during their break and meal period.
Results: There were 534 shifts (10.2%) where participants reported having no chance to take a break or sit down for a meal during their shift, and 2248 shifts (43.1%) where they reported getting some time for a break or meal period but were not relieved of patient care responsiblili-

ties. Nurses reported having a break or meal period free of patient care responsibilities less than half the shifts they worked (2429/5211 shifts). Breaks and meal periods averaged only 23.8 ± 30.1 minutes, even though 39% of the shifts exceeded 12.5 hours. Shift duration did not affect duration of breaks and meal periods. The mean duration for breaks and meal periods was 23.4 ± 28.5 minutes for shifts of 8.5 hours or less, 22.3 ± 27.9 minutes for shifts longer than 8.5 hours but less than 12.5 hours, and 25.5 ± 33.0 minutes for shifts ≥ 12.5 hours. There were no differences in the number of errors or episodes of drowsiness reported by nurses who were able to take a break or meal period free of patient care responsibilities and those who did not get a break or meal period free of patient care responsibilities. However, night shift nurses who were able to take a break or meal period free of patient care responsibilities reported significantly more episodes of falling asleep during their shift than night shift nurses who did not have a break or meal period free of patient care responsibilities (OR=0.46, p =0.02), suggesting the possiblity that at least some of the night shift nurses may have napped during their break periods.
Conclusion: These finding support earlier reports that nurses frequently skip their breaks and meal periods to provide patient care. Although this practice is undesirable, it was not associated with an increased risk of errors or greater numbers of drowsy episodes.

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Sleep Disturbances and Quality of Life by Ethnicity in the Sleep Heart Health Study

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Introduction: The goal of this exploratory study is to describe sleep disturbances and quality of life (QoL) of African American (AA), southwestern U.S. Latino, and non-Hispanic white (NHW) participants in the multi-center Sleep Heart Health Study (SHHS).
Methods: SHHS participants underwent home polysomnography, completed the SF-36 health survey, and the SHHS Sleep Habits Questionnaire (SHQ), which included the Epworth Sleepiness Scale (ESS). Physical (PCS) and Mental (MCS) Composite Scales were scored from SF-36 responses. The PCS indicates physical functioning aspects of QoL, while the MCS indicates overall mental health. Higher scores indicate better QoL. Sleep disordered breathing (SDB) was defined as respiratory disturbance indices >=5 apneas or hypopneas/hour, with each event associated with >=4% desaturation (RDI 4%). Participants who selected "often" and "almost always" responses for trouble falling asleep, staying asleep, or early morning awakening categories of the SHQ were defined as having difficulty initiating and maintaining sleep (DIMS). Excessive daytime sleepiness (EDS) was noted in participants scoring >10 on the ESS (range 0-24). Standardized scores were calculated for PCS and MCS and adjusted for sex, age, education and BMI. Statistical analysis was performed using ANOVA with significance level set at $p<0.05$.
Results: There were 5,738 SHHS participants, 53% women; 86% NHW; 9% AA; 5% Latino. Mean age was 63±11.2 years; mean education 14±3.4 years; mean BMI 28±5.2 kg/m2. Subgroups of participants with sleep disturbances were defined in 3 different ways: SDB (n=2,147); DIMS (n=1,420); and EDS (n=1,164). PCS scores were lower for AA compared to NHW for each of the three different sleep disturbances ($p<0.001$). The mean PCS comparing AA to NHW with SDB was 43.3±11.8 vs. 46.3±10.1, with DIMS was 41.6±12.5 vs. 45.4±10.5, and with EDS was 42.8±11.8 vs. 46.5±10.3. AA with DIMS reported lower PCS compared to Latinos with DIMS (41.6±12.5 vs. 45.3±10.2, $p<0.05$). There were no differences in mean PCS between AA and Latinos with SDB (43.3±11.8 vs. 45.3±10.1) or EDS (42.8±11.8 vs. 45.7±10.7) respectively. NHW and Latinos did not differ on PCS scores for any of the sleep disturbance subgroups. MCS scores for SDB showed AA (52.3±9.0) and Latinos (51.6±9.4) to have lower scores compared to NHW (53.8±8.0, $p<0.05$). MCS scores for DIMS were also lower for AA (49.1±10.0) and Latinos (47.0±10.6) compared to NHW (51.8±9.0, $p<0.05$). Latinos with EDS (48.1±10.9) showed lower MCS scores compared to NHW participants with EDS (52.1±8.6, $p<0.01$), but did not differ from AA with EDS (50.8±9.8).
Conclusion: Preliminary findings of subgroup analyses suggest that AA with any sleep disturbances (defined in three different ways) report greater impairment of their physical functioning than their Latino or NHW counterparts. Both AA and Latinos with sleep disorders report impairments in the mental health domain. Despite the high prevalence rate for DIMS in the NHW group (26% to AA 3% and Latino 2%), these participants indicate better QoL compared to the AA and Latino cohorts. Findings may be related to differences in social support, access to care, other comorbid conditions, or other factors that require further investigation.

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The Relationship between Sleepiness and Obesity in a Non-clinical Population

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Introduction: Obesity and daytime sleepiness are serious contemporary concerns. The relationship between obesity and sleepiness is not fully understood. There is clear evidence to suggest that obesity is linked to sleepiness in that obesity is a significant risk factor for obstructive sleep apnea with resulting sleep disruption and sleepiness. The impact of sleepiness on obesity is less clear. Our objective was to examine the relationship between obesity and daytime sleepiness in a non-clinical population, as well as to explore potential mediating variables such as chronotype, sleep quality, or demographic variables.
Methods: 299 university students (102 male, 197 female) aged 17 to 49 years (M=21.6, SD=5.5) completed questionnaire packets including demographic information, weight, height, Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index, and Horne-Ostberg Morningness/Eveningness Questionnaire (HOMEQ). All subjects denied diagnosis of any sleep disorders.
Results: BMI (M=24.34; SD=5.04) and ESS (M=9.95; SD=4.09) were within expected ranges for a college population. Although the correlation between BMI and ESS for the entire sample was not significant ($r(297)=-.027$; $p>.05$); this relationship was significant for some subsets of the sample. There was a significant positive correlation between BMI

and ESS for both the excessively sleepy subset (ESS>14; r(35)=.436; p<.05) and those subjects identified as morning types (HOMEQ> 58; r(33)=.295; p<.05). A 2X3 factorial ANOVA (morning and evening types; below average, average, and excessively sleepy) yielded a significant interaction between chronotype and sleepiness on BMI (F(2,117)=3.44; p<.05); showing a significant increase in BMI with increasing sleepiness levels for morning types that was not present for evening types.

Conclusion: For excessively sleepy individuals (ESS>14) a positive correlation between sleepiness (as measured by the ESS) and obesity (BMI) existed. For the general population the relationship between sleepiness and obesity was present only for morning types. It has been suggested that sleepiness may be related to obesity through declines in physical activity, and/or through increased eating behavior to combat subjective sleepiness or to maintain homeostatic balance. It follows that within the sleepy population, with increasing sleepiness comes an increasing vulnerability to obesity. It is hypothesized that until some threshold in sleepiness is met, compensatory mechanisms are not expressed explaining why this relationship is only observed in the excessively sleepy group. It is not clear why the relationship between sleepiness and obesity manifests itself in morning types only. Sleepiness in obese patients has been suggested to be primarily a manifestation of abnormal circadian or metabolic processes with associated hypoarousal during the day and hyperarousal during the night. It is suggested here that this obesity related homeostatic imbalance may be exacerbated in morning types and/or that morning types are especially vulnerable to this arousal shift compared to evening types. Because this misalignment is in contrast with the typical behavioral patterns of morning types it may be that obesity associated hypoarousal in the early part of the day produces increasing levels of sleepiness which may lead to increased eating as well as decreased activity for heavier morning types while not so for normal and underweight morning types.

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Sleep-Dependent Learning And Motor-Skill Complexity

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Introduction: Several studies have now shown that, following training on a sequential motor-skill task (SMST), subsequent improvements develop exclusively during sleep [Walker-2002, 2003; Fischer 2002]. This sleep-dependent learning occurs regardless of whether the sleeping episode occurs during the day or night, with the delayed improvements correlating with a specific sleep-stage window [Walker-2002]. However, these studies only describe the features of motor learning using a short unimanual, motor sequence, and have not considered how sleep-dependent learning may change when the motor-skill becomes more complex. Since the majority of motor skills we acquire are complex and multi-limbed, it is imperative to understand potential differences in sleep-dependent learning across a spectrum of motor-skill difficulty.

Methods: We investigated differences in sleep-dependent motor-skill learning by varying two characteristics of the SMST (1) the limb complexity—either unimanual or bimanual, and (2) the sequence length—either 5-elements or 9-elements. Subjects (n=60, all right-handed) were assigned to 4 groups (n=15/group): Uni-5: Unimanual, 5-element sequence (four fingers on one hand) Bi-5: Bimanual, 5-element sequence (four fingers, two from each hand) Uni-9: Unimanual, 9-element sequence (four fingers on one hand) Bi-9: Bimanual, 9-element sequence (eight fingers, four from each hand) Subjects were trained on Day-1, and retested following one night of sleep on Day-2. Quantitative measures were the number of complete sequences ("Speed"), and the number of errors made relative to the number of correct sequences ("Accuracy") in 30-s trials. An additional qualitative measure investigated the mean reaction times between each successive key-press transitions within the sequence ("Transition Speeds").

Results: Following training on Day-1, significant improvements in speed and accuracy developed following sleep at retest on Day-2 for all groups (Speed: p<0.0006; Accuracy: p<0.05). Although improvement was common across all groups, the amount of improvement differed between groups, determined by the task characteristics. While the Uni-5, Bi-5, and Uni-9 groups, all using four fingers, showed similar 18-20% overnight improvements in speed, the Bi-9 group, using eight fingers, showed a considerably larger 29% speed improvement. Overnight improvements in accuracy were similar across all groups. Looking within each sequence, across all groups, there were specific key-press transitions where individual subjects were slow (difficult transitions) and others where they were fast (easy transitions). Remarkably, when these transitions were analyzed after a night of sleep, only the difficult transition showed overnight improvements (p<0.0001 for all groups), while the easiest transitions showed no such improvement.

Conclusion: These data firstly suggest that as motor skill complexity increases, so too does the amount of subsequent overnight, sleep-dependent improvement, most likely due to the greater amount of cortical mass engaged during the task (eight fingers vs. four). Secondly, the sleep-dependent benefit appears to selectively favor regions of the motor-sequence program that were most difficult prior to sleep, while leaving the already efficient segments of the motor-sequence program unchanged.

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Sleep-Dependent Plasticity And Motor Skill Learning In The Human Brain

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Introduction: Behavioral studies in humans have shown that learning of a sequential motor skill task (SMST) involves several discrete memory stages. Following practice, periods of wake allow the memory to become stable and resistant to interference, but do not result in any further learning improvements [Walker-2003]. In contrast, a subsequent night of sleep triggers additional learning benefits without further practice, resulting in increased speed and accuracy the following morning [Walker-2002, 2003; Fischer 2002]. Despite these findings, the underlying neural correlates of sleep-dependent motor learning remain unknown. Here we report fMRI data directly comparing functional brain activation after episodes of either sleep or wake following training on the SMST.

Methods: Subjects (n=12; all right-handed) underwent a repeated measures protocol involving two phases. In one phase, subjects were trained on a specific motor sequence in the evening using their left, non-dominate hand. Twelve hours later, following a night of sleep, subjects were retested on the motor sequence during fMRI scanning ("SLEEP-protocol"). In the other study phase, subjects were trained on a different motor sequence, again using their left hand, this time in the morning. Twelve hours later that evening, without intervening sleep, subjects were retested on the motor sequence during fMRI scanning ("WAKE-protocol").

The two phases were separated by one week, and performed in a counter-balanced order across subjects. Thus, for each subject, two functional brain activation maps were produced 12hrs after motor skill training, once after 12 hr containing a night of sleep, and once with no intervening no sleep.
Results: When activation maps from the SLEEP-protocol were contrasted with those from the WAKE-protocol (SLEEP > WAKE), regions of increased activation were observed in the right primary motor cortex (M1), right medial-frontal lobe and left cerebellum. Surprisingly, there was also a region of increased activation in the right hippocampus. The opposite contrast (SLEEP < WAKE) revealed decreased activity after sleep bilaterally in the parietal lobes (both inferior and superior regions), as well as in occipital-temporal junctions.
Conclusion: These findings describe a highly complex pattern of sleep-dependent functional brain plasticity. We believe that the increased activation of the primary motor cortex and cerebellum, likely explains the greater performance speed and accuracy following a night of sleep described in previous behavioral studies [Walker-2002, 2003; Fischer 2002]. In addition, increased activation of the medial-frontal regions would allow improved online evaluation of motor performance [Koechlin-2002; Schlaug-1994] post-sleep, while the enhanced hippocampal activity may reflect the increased demands for temporal sequential control of finger movements. At the same time, decreased activity in the parietal and posterior temporal lobes likely reflects the greater automaticity of the task, thus reducing attentional demands and conscious monitoring of spatial relationships between finger movements and position.

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The Functional Anatomy Of Sleep-Dependent Visual Skill Learning
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Introduction: Learning of procedural skills is a gradual process. While practice improves performance during training, learning continues to develop in the absence of further practice, and these delayed improvements occur specifically across episodes of sleep [Stickgold-2000; Walker-2002]. Here we report fMRI evidence for bi-directional changes in brain plasticity occurring exclusively across a night of sleep following training on a sleep-dependent visual texture discrimination task (TDT).
Methods: Based on the retinotopic and monocular specificity of this TDT, we were able to investigate, in the same subjects (n=18), during the same scanning session, at the same circadian time, how functional brain activity and learning changed at retesting following a night of sleep (SLEEP), compared to retesting without intervening sleep (NO-SLEEP). Subjects were trained monocularly on the TDT in the lower right quadrant of the visual field using either the left or right eye in the evening on Day-1. The following morning, on Day-2, subjects were trained in the same lower right quadrant of the visual field using the other eye. All subjects received equal amounts of training in the same visual field using each eye. Immediately after training of the second eye on day-2, each eye was then retested separately and monocularly in the trained quadrant of the visual field during fMRI scanning. Thus, testing of one eye was after training of that eye followed by a night of sleep, and testing of the other eye was after training with no intervening sleep.
Results: At retest, fMRI group-analysis demonstrated significantly increased activation in the left primary visual cortex (V1, corresponding to the trained visual-field) in the SLEEP condition, relative to the NO-SLEEP condition. This is similar to findings comparing trained and untrained eyes, 24hrs after the training of one eye [Schwartz-2002]. Surprisingly however, we found additional regions of lateralized increased activity beyond V1, including the left medial temporal lobe and left superior and inferior parietal lobe. Furthermore, that was a region of decreased activity in the right temporal pole region.
Conclusion: These data provide evidence of sleep-dependent brain reorganization across a single night of sleep, suggesting that learning of this sleep-dependent task is associated with plasticity in known visual identification pathways of the human brain [Ungerleider-1994]. We hypothesize that the sleep-dependent increases in V1 activity drive concomitant increases in downstream regions related to both attention and object recognition, while the increased ease of the task following sleep reduces emotional task demands, thereby reducing activity in the temporal pole.

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Does The Maintenance Of Wakefulness Test (MWT) Relate To Driving Simulator Performance?
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Introduction: The MWT, a test of vigilance in a soporific environment, is used clinically in Australia to assess fitness to drive. Very few studies have actually examined the relationship between the MWT and driving performance. This study examined the ability of the MWT to predict driving simulator performance in healthy individuals.
Methods: 20 healthy, young volunteers underwent two nights of testing (preceded by a sleep restriction night) one week apart. The MWT was included as part of an experimental protocol which examined the effect of low alcohol consumption and sleepiness on driving simulator performance. MWT mean sleep latency and driving simulator performance were examined under two conditions: Sleep restriction (SR) and a combination of sleep restriction and alcohol consumption (SRAL). Alcohol consumption was randomized to one of the test nights. Subjects underwent two MWT 40 minute trials (1st at 11:30pm; 2nd at 2:15am) either side of the driving task. At 1am, subjects began a 70-minute AusEd driving simulation task. During the driving task subjects were monitored continuously with EEG. Mean cumulative microsleep (micslp; >3 secs bursts of theta) and the driving simulator parameters, steering deviation from median lane position (StD), reaction time (breaking to avoid a vehicle on the roadway; RT) and crashes (off road, stoppage or rear ending another vehicle) were used in the analysis.
Results: MWT mean sleep latency did not differ between conditions ($p=0.09$) but did by time of night ($p<0.001$) with shorter sleep latencies at 2:15am versus 11:30pm. In the SR condition MWT mean sleep latency correlated with RT ($p=0.03$). MWT sleep latency at 2:15am correlated with micslp ($p=0.02$) and StD ($p=0.02$) during the last 20 mins of the driving task. During the SRAL condition all parameters correlated with MWT mean sleep latency (micslp, $p=0.02$; StD, $p=0.02$; RT $p=0.02$; Crash $p=0.05$).
Conclusion: During periods of greater sleepiness (2:15am) and after alcohol the MWT correlates with driving simulator measures. The MWT explained 20-33% of the variance of driving performance impairment.

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The Effects of Performance Feedback From Actigraphy on Sleep Hygiene in Rail Transportation Workers

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Introduction: The of this project goal was to determine whether actigraphs that produced continuous estimates of performance effectiveness on the monitor face could be useful for helping railroad employees better manage their sleep and wake activity. Participation consisted of the completion of several questionnaires, a sleep log, and wearing an actigraph, which measured sleep and work activity.
Methods: Twenty-nine individuals originally agreed to wear an actigraph sleep watch, 24 hours a day, for two consecutive thirty-day periods. Participants also completed a daily sleep log and a packet of additional measures from the Shiftwork Index and other sources. Age ranged from 22 to 65, with a mean of 41. Average number of years of education was 13.29, with the average tenure as an employee being 13.97 years. Eight participants discontinued participation during the first month, thus a total of 21 participants completed this study. During the baseline period, all participants wore the same type of non-performance actigraph to gather baseline activity data. At the end of the thirty-day baseline period, sleep logs were collected and a survey was administered. At this time, performance monitoring actigraphs were randomly distributed to half of the sample. The performance feedback/monitoring actigraphs displayed a number that corresponds to estimated individual effectiveness. This displayed number is based on an algorithm programmed into the memory chip that uses the actigraphy information to calculate an estimated performance effectiveness score. The algorithm is based on the research of the Walter Reed Army Medical Center sleep performance model. Ten participants received the performance watches and eleven received the non-performance watches. Individuals who received the performance watch were given instruction on how to interpret the performance reading, as well as instruction on fatigue countermeasures.
Results: Seven out of nine participants wearing the performance actigraph reported that the device helped them monitor fatigue ($F(10, 18)= p<.038$) to a greater degree than those wearing non-performance feedback actigraphs. Similar findings were also noted for the management of fatigue as well as increased awareness of fatigue. In addition, significant differences between feedback and non-feedback groups were noted in mood and sleepiness ratings. While no significant differences in overall amount of sleep were found, analyses of the obtained sleep indicated lower variability in sleep duration for those wearing the performance feedback devices. Specifically, the standard deviation of sleep minutes for the performance feedback group was 99.94 minutes and 163.32 for the non-feedback group, a difference that was significant using Levenes test of equality of variances ($p<. 024$). Variability of percentage of sleep was found to be 7.24 percent for the performance feedback group and 11.33 for the non-feedback group ($p<.035$).
Conclusion: Overall, participants using the performance feedback devices found them to be useful for fatigue management, reported some improvements in mood and sleepiness, and obtained more consistent sleep duration.

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What People Associate with the Moment of Drowsiness

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Introduction: In November 2002, the National Sleep Foundation sponsored the Drowsy Driving Summit to be followed by the "National Action Plan to Prevent Drowsy Driving." However, a widely accepted consensus regarding the definition of subjective drowsiness remains elusive. Clearly the National Action Plan, and the public as well, would greatly benefit from an unambiguous definition of the term which could be widely publicized. One approach that has been utilized to address this problem is simply to ask individuals what feelings they associate with being drowsy. If an accurate and easy to recognize definition of drowsiness were established, it would help drivers and other individuals at risk to identify the onset of drowsiness and avoid the danger of the associated impairment of attention, alertness, and reaction time.
Methods: A detailed questionnaire is being administered to small groups of Stanford University undergraduates in the dormitories at 6 PM prior to an hour-long talk by one of the investigators (WCD). This instrument assesses what psychological and behavioral feelings the respondents associate with being drowsy. The average group size has been 32 students. To date, 191 questionnaires have been completed. This activity will continue throughout the academic year with an eventual target of several thousand Stanford undergraduates.
Results: Preliminary data reveal that the Stanford population originates from diverse ethnic, socioeconomic, and geographic backgrounds from across the U.S. and world. Students defined drowsiness as: 1) 13.73% - I can't keep my eyes open or my eyelids are heavy, 2) 12.81% - I want to close my eyes, 3) 12.19% - It is more difficult than usual to pay attention and/or concentrate, and 4) 9.32% - I have less energy than usual. The categories least indicative of drowsiness were: 1) My arms feel heavy (1.54%), and 2) I don't feel like moving (4.10%). The categories with moderate response were: 7.89% - I want to lie down, 6.97% - I did not get enough sleep the previous night, and from 6.56-6.35% - It's difficult to hold my head up, I lose interest in doing anything except sleeping, and I start yawning. There were 976 total responses.
Conclusion: This study finds that the moment of drowsiness is most often associated with a physical feeling involving the eyes, and behaviorally, with a decreased ability to remain attentive. The physical feeling of a heaviness of the eyes is the most useful as it can be used to define a relatively precise moment of drowsiness onset. To these ends, an effort to establish a commonly accepted definition will also result in an increased awareness about the importance of sleep. By being able to recognize the onset of drowsiness with accuracy, the public will have a clear signal of when to stop driving. As people are educated to identify the dangerous moment of sleepiness, the public will also become more aware about sleep and its implications.

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The Role of Context in Differential Sleep Architecture Changes Following Footshock

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Introduction: Fearful stressors affect sleep in humans and animals. We, and others, have previously demonstrated that both the presentation of mild footshocks and reexposure to the context in which footshocks were presented suppress REM sleep (REMS) selectively over several subsequent hours. In this study, we examined rats' sleep-wake response to

footshock 24 and 48 h after a single training session. To our knowledge, this represents the first time sleep architecture changes resulting from a single session of shock training (ST) have been examined in a neutral context beyond 24 h in rats. We also studied how reexposure to the context in which footshocks were presented modulates the sleep-wake response to a fearful stressor at these time points.
Methods: Electrodes for recording EEG and EMG were implanted into 13 male Sprague-Dawley rats. Following at least 7 days of recovery, animals were habituated to a recording chamber (neutral context) for 4-6 hours over 5-7 days. On the next day, baseline sleep was recorded over 4 h (11 AM - 3 PM) in the neutral context. One day later, animals were trained with 5 footshocks (0.5 mA, 0.5 sec) administered over 30 min in a second, distinct recording chamber ('unsafe' context). Sleep was recorded on the following day, over 4 h, in either the neutral (ST/N group, n=6) or the unsafe (ST/U group, n=7) context. Subsets of animals (ST/N, n=6; ST/U, n=3) were reassessed one day later, in the neutral or unsafe context, respectively. We measured sleep efficiency (SE; time spent asleep/total recording period), average hourly REMS time (REMS-A), average hourly non-REMS time (NREMS-A), and average hourly wake time (WAKE-A). Values are presented as percentage of baseline values. Data were analyzed with repeated measures ANOVA.
Results: The ST/N group displayed a non-selective increase in sleep (SE: 109%, $p<0.05$; REMS-A: 118%, n.s.; NREMS-A: 104%, n.s.; WAKE-A: 87%, $p<0.05$) on the day following training. Interestingly, a greater, and relatively selective non-REMS increase was seen on the second post-training day (SE: 118%, $p<0.05$; REMS-A: 125%, n.s.; NREMS-A: 129%, $p<0.05$; WAKE-A: 75%, $p<0.05$). As expected, the ST/U group showed a relatively selective REMS decrease on the first post-training day (SE: 81%, $p<0.005$; REMS-A: 46%, $p<0.0005$; NREM-A: 86%, n.s.; WAKE-A: 132%, $p<0.005$). Second post-training day studies in a small subset of the ST/U group suggested that the REMS-selective decrease persisted.
Conclusion: Rats' sleep in a neutral context 24 h following footshock presentation was characterized by a non-selective increase in SE and, 48 h later, by a relatively selective increase in non-REMS. The suppression of REMS observed in the unsafe context 24 h after exposure to footshock demonstrates rats' ability to differentiate between the two contexts and is evidence of contextual fear conditioning. Fear conditioning in animals has been viewed as a means of modeling anxiety disorders in humans. Thus, the alteration of the normal rodent sleep-wake response to footshock presentation by reminders of the aversive stimulus may provide a window into the pathogenesis of prolonged sleep disturbances associated with anxiety disorders, including posttraumatic stress disorder, in humans.

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Epworth Sleepiness Scale Scores And Use Of Drugs In First Year University Students

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Introduction: It is widely accepted that chronic partial sleep deprivation is prevalent among adolescents and young adults. Among the most common correlates of this insufficiency of sleep are daytime sleepiness and the use of psychoactive substances. Significant relationships between the use of psychoactive substances and sleep habits and perceived fatigue have been reported. The aim of this presentation is to study the relationship between the use of psychoactive drugs and daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS).
Methods: Subjects: Self-reported information was obtained from questionnaires administered to first year students of the Universidad Autonoma, Madrid, Spain. A total of 1714 were given, in a in-class survey, the questionnaire. Of those 1391 (81%) completed it. The percent of men was 26.2; the mean age was 18.74 (+-1.24) years with a range of 16-23. Questionnaire: The questionnaire includes: (1) socio-demographic information, (2) Sleep environment, (3) Sleep habits, (4)Horne and Ostberg Questionnaire, (5) Sleep disorders, (6) Epworth Sleepiness Scale, (7) Life style, including physical activity, use of psychoactive drugs and eating habits, (8) Health status, (9) Academic performance, (10) Recent events and behavior. Statistical analysis: Pearson Chi-square with Yates correction or Fisher exact probability test was used. To study the relation between quantitative variables and qualitative ones we checked the normality of the sample by using Kolmogorov-Smirnov test. In case of non-normality U of Mann-Whitney and H of Kruskal-Wallis were used. The significance level was established at $p<.05$.
Results: Use of therapeutic drugs: analgesic (20.3%), tranquillizers (5.9%), hypnotics (3.8%). Use of non-therapeutic drugs: alcohol (77.6%), tobacco (34.3%), coffee (60.2%), tea (28.2%), colas (70.2%), cocaine (2.2%), amphetamine (0.5%), ecstasy (1.3%), design pills (2.1%), marijuana/hashish (22.1%), LSD (0.8%), inhalants (0.4%). None of them reported to use heroine or methadone/LAAM. Mean score in the ESS was 8.85 (+-3.3) for the whole sample, with 29.6% of the subjects having a score higher than 10, 24.9% of the men and 31.3% of the women scoring above that threshold ($p<.022$). As for the relationships between score in the ESS and the use of drugs there were statistically significant associations for: alcohol ($p<.006$), cannabis ($p<.000$), colas ($p<.021$), tobacco ($p<.054$), analgesics ($p<.012$) and hypnotics ($p<.027$).
Conclusion: The data of our study suggest that self-reported daytime sleepiness as assessed by the ESS is significantly associated with the use of various depressant and stimulant psychoactive substances in a sample of first year university students. The use of depressants could be a contributing factor to the presence of daytime sleepiness, whereas that of stimulants could be an attempt to mitigate it.

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Sleepiness Increases Lapses Due To Distraction

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Introduction: Without stimulation sleepy people are more liable to fall asleep. To avoid tedium, and remain awake, they seek alternative stimulation, especially when the task in hand is boring and monotonous. Sleepiness at a dull task is indicated by 'lapses', usually attributed to microsleeps. However, in moderately sleepy people some 'lapses' may be due to self-generated distractions, and not to microsleeps. It may be argued that it does not matter whether a lapse is a distraction or a microsleep, as both are due to sleepiness and result in a delayed/missed response. Alternatively, we propose that distraction lapses result from a lesser degree of sleepiness, and if regarded as microsleeps, will indicate that the subject is more sleepy than might be the case. We investigated the incidence of distraction lapses as a consequence of sleepiness.
Methods: Sixteen healthy, young (range 21-23y), screened good sleepers (8±1h), without daytime sleepiness (<2naps/month and ESS scores <10), underwent a 30 min psychomotor vigilance test (PVT) at 15:00h, in a repeated measures 2x2 counterbalanced design, with two sleepiness conditions (normal sleep Vs restricted sleep [2am-7am]) and distraction Vs no distraction. Distraction comprised a video in the visual periphery, showing an episode of a popular TV show. Subjects had to ignore this

and attend to the PVT. For 'no-distraction', the TV was off. Lapses (>500msecs) were logged and distractions assessed from a video camera on the subjects' faces (e.g. head turn).
Results: Repeated measures ANOVA on the lapses (irrespective of cause) showed significant effects of sleep Vs sleep restriction ($p<0.05$) and distraction Vs no distraction ($p<0.04$), as well as a significant interaction ($p<0.01$), with sleep restriction + distraction producing the most lapses. An ANOVA on the distractions alone, revealed significantly more distractions under: sleep restriction ($p<0.02$); distraction ($p<0.02$); and for the interaction (sleep restriction + distraction $p<0.02$). Interestingly, when comparing the two nil-distraction conditions there were more spontaneous distraction lapses (i.e. the subject just looking around) during sleep restriction.
Conclusion: Sleepiness increases lapses on the PVT due to distraction. Although lapses are generally attributed to micro-sleeps, we find in moderately sleepy people that a significant proportion of these 'lapses' are 'distractions'. However, as sleepiness worsens more of these distractions are probably replaced by true microsleeps. These distraction-lapses due to the participant seeking stimulation when moderately sleepy and/or during monotony or boredom, may help explain apparently paradoxical findings where increased lapses are reported in sleep satiated participants undergoing prolonged and tedious experimental regimens.

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High Sugar Intake Exacerbates Sleepiness

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Introduction: Some non-caffeinated drinks contain very high levels of sugars (usually glucose and sucrose), with the general assumption that this combats not only physical and mental fatigue, but also sleepiness. However, little is known about the latter effect. Although there may be an initial improvement in alertness following immediate absorption of sugars these drinks, few studies go beyond 30 min of assessment following intake. Previous work from our laboratory points to a significant increase in subjective sleepiness beyond this 30 min point, when 60g of dissolved sugar is drunk - the effect being greatest at the circadian mid-afternoon 'dip' in alertness (c. 15:00h). However we have no performance data to back this up. We investigated this apparent sleepiness further using the psychomotor vigilance test (PVT).
Methods: Ten healthy, young participants (mean: 22.4y ± 1.4y), BMIs of 22-25, underwent a night of sleep restriction (02:00-07:00h) to exacerbate the post-lunch dip. Commencing at 14:00 they underwent three, 30 min periods of PVT, separated by two, three minute breaks and with two counterbalanced conditions: i) nil-sugar (artificial sweetener) version of a ii) high-sugar (42g sucrose and glucose) content fruit flavoured drink. Drinks were given double blind and consumed at 13:50h. Prior food intake was controlled with participants refraining from eating from 09.30h that morning and they were given a standard, light lunch, in the laboratory, at 12.30h. They remained in the laboratory from lunch until completion of the PVT. We assessed the incidence of 'lapses' (>500msec) throughout the 90 min of testing.
Results: Overall, there were significantly ($P<0.007$) more lapses during the sugar condition. A two-way ANOVA on the data broken into 3x30minute blocks found the effect to be most marked in the third block, which coincided with the afternoon 'dip'.
Conclusion: We found that sleepiness-related PVT impairment during the mid afternoon was exacerbated following a bolus intake of sugars. This 'sugar effect' was greatest around 60-90 min after consumption and at the mid afternoon 'dip'. We suspect that the mechanisms behind this are linked to the surge in insulin output and other sequelae (e.g. increased brain 5HT synthesis).

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Sleep And Auditory Learning

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Introduction: Sleep between sessions of visual perceptual and motor learning tasks results in greater performance improvements compared with waking. Few studies have investigated effects of sleep on auditory learning. A fundamental question is whether sleep specifically promotes learning, or whether resting yields similar benefits. The "interference hypothesis" postulates that sleep promotes learning by preventing interference from ongoing sensory input, learning and other cognitive activities that occur during waking. We tested this hypothesis by comparing effects of sleep, waking, and resting on auditory tone sequence learning.
Methods: Subjects (n=64) were right-handed 18-28 year-olds with normal hearing thresholds. For three days before the study they maintained a regular sleep schedule (23:00-07:00, verified by wrist actimetry), refrained from napping, and abstained from alcohol and caffeine. They completed two sessions of a challenging auditory perceptual learning task that required identification of complex auditory patterns. Between sessions, there was a two hour experimental period in which subjects were instructed to sleep (sleep group), to lie in the dark without sleeping (rest group) or to watch an educational film (wake group). Another group of subjects completed two immediately consecutive sessions (no break group). Subjects were randomly assigned to groups (n=16 per group), with the constraints that the groups were matched in age and half of the subjects in each group were females. The sleep, rest, and wake groups underwent polysomnographic recordings during the experimental period. The wake group was supervised and the physiological signals of the rest group were monitored to ensure that subjects did not sleep. The second learning test began 65 min. after the end of the experimental period. Behavioral performance was quantified with a learning score that assessed performance accuracy.
Results: The sleep group had a total sleep time of 77.1±5.6 min.. The change in learning scores from session 1 to session 2 differed among groups, as indicated by a significant group * session interaction ($F(3, 60)=3.61$, $p=0.02$). Mean performance changes were 0.92±0.15, 0.65±0.15, 0.26±0.16, and 0.61±0.12 in sleep, rest, wake, and no break groups. Sleep, rest, and no break groups showed significant improvement from session 1 to session 2 (sleep: $p<0.0001$, rest: $p<0.001$, no break: $p<0.001$), whereas the wake group did not. The performance increases in the sleep, rest, and no break groups did not differ and were significantly larger than in the wake group (sleep vs. wake: $p<0.01$; rest vs. wake: $p<0.05$, no break vs. wake: $p<0.05$). The groups did not differ in initial performance or reaction speed. Reaction speed (1/reaction time) increased from session 1 to session 2 ($F(1, 60)=15.47$, $p<0.001$). This change did not differ among groups.
Conclusion: Compared with waking, sleep and rest facilitated learning of auditory patterns. Furthermore, subjects with no break between learning sessions also showed performance improvements. These findings support the hypothesis that sleep and rest promote auditory learning by reducing interference that occurs during waking. They suggest that a dark, quiet environment, reduced sensory and cognitive interference, and physiological changes that accompany rest can largely account for the facilitation of auditory learning that occurred during sleep.

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Individual Differences In A Daytime Nap: A More Powerful 'Power' Nap In Habitual Nappers

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Introduction: A short nap improves alertness and performance. Many adults habitually nap while others rarely or never nap despite opportunity to do so. We hypothesized that habitual nappers may experience greater benefits from napping in terms of well-being and performance. To examine this, we compared sleep architecture and quantitative EEG characteristics in a 20-minute afternoon nap in habitual and non-habitual nappers.
Methods: A survey on napping behaviour was completed by 137 undergraduates. Twenty respondents (mean age = 20.7) who were healthy, good sleepers were invited to participate in a napping study. Habitual nappers (n = 12) were those who napped 'once or twice a week' or 'every day'; non-habitual nappers (n = 8) napped 'once or twice a month' or 'never'. In lab, participants were given a 20-minute nap opportunity (14:40 h to 15:00 h). Sleep was scored using standard criteria. Less than 50% alpha per epoch defined Stage 1a; the presence of theta and/or vertex sharp waves defined Stage 1b. EEG was sampled at 256Hz from 20 sites and re-referenced offline to an average of A1+A2. The first 2-minutes of artifact-free EEG for each sleep stage was submitted to power spectral analysis for midline sites (Fz, Cz, Pz, Oz). Frequency bands were defined as delta (1-4 Hz), theta (4-8 Hz), low alpha (8-10 Hz), high alpha (10-12 Hz), low sigma (12-13.5 Hz), high sigma (13.5-15 Hz), and beta (15-25 Hz).
Results: Survey data: 18.2% of respondents napped every day, 51.8% once or twice a week, 22.6% once or twice a month, and 6.6% never. As well, 33.6% of the sample reported napping due to excessive sleepiness, 27.0% took prophylactic naps, 43.8% took appetitive naps, 81.0% took replacement naps, and 49.6% napped due to chronic sleep restriction. Nap data: Sleep efficiency was 69.76% for all participants. Habitual and non-habitual nappers did not differ in stage latencies nor percentage time in stage. Stage 1: habitual nappers had greater power for low alpha at Fz, $t(16)=2.45$, $p=.03$; Cz, $t(16)=2.57$, $p=.02$; Pz, $t(16)=2.53$, $p=.02$; and Oz, $t(16)=2.57$, $p=.02$; and high alpha at Fz, $t(16)=2.76$, $p=.01$; Cz, $t(16)=3.47$, $p=.003$; Pz, $t(16)=4.03$, $p=.001$; and Oz, $t(16)=2.91$, $p=.01$. Stage 2: habitual nappers had greater power for delta at Fz, $t(14)=2.80$, $p=.01$; and Cz, $t(14)=2.32$, $p=0.04$; low alpha at Fz, $t(14)=2.35$, $p=.03$; and Cz, $t(14)=2.15$, $p=.05$; high alpha at Fz, $t(14)=2.16$, $p=.049$; Cz , $t(14)=2.21$, $p=.045$; and Pz, $t(14)=2.35$, $p=.03$; low sigma at Cz, $t(14)=2.27$, $p=.04$; and Pz, $t(14)=2.47$, $p=.03$; and high sigma at Cz, $t(14)=2.31$, $p=.04$.
Conclusion: Individual differences in napping behaviour can be identified in the population. Self-identified non-habitual nappers slept as well as habitual nappers according to gross sleep architecture. However, habitual nappers had greater delta, alpha, and sigma power than non-habitual nappers. The sleep EEG might predict differential improvement in alertness, mood, and performance for habitual and non-habitual nappers.

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Sleep Spindles and Sigma Power Predict Motor Performance Improvements Following a Short Nap

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Introduction: A short nap has been found to improve alertness, attention, psychomotor performance, and restore perceptual learning performance. We reported that habitual nappers and non-habitual nappers did not differ in sleep architecture during a daytime nap, but habitual nappers had greater EEG power in delta, alpha, and sigma frequencies. We therefore investigated FFT predictors of motor procedural learning performance following a nap in habitual and non-habitual nappers. We hypothesized that sleep spindles and sigma power might predict motor performance, since spindles have been found to increase following intense periods of motor procedural learning.
Methods: Participants were 20 young adults, age 18-30 (M=20.7, 11 male), without medical, psychiatric or sleep difficulties. Habitual nappers (n = 12) were those who napped 'once or twice a week' or 'every day'; non-habitual nappers (n = 8) napped 'once or twice a month' or 'never'. Participants performed a simple motor procedural learning task before and after a 20-minute nap. Improvement on the motor task involves implicit learning of procedural movements that are cognitively simple. Each trial consisted of an attempt to catch a ball (3cm) with a cup (3.5cm) that is attached to the ball by a string (30cm). Performance was scored on a 4-point scale from 0 (miss) to 3 (catch), over 200 trials in each session. Post-nap testing took place 30-minutes after awakening to avoid sleep inertia. FFT values at Cz from the first 2 minutes of Stage 2 sleep were used in this analysis. Spindle activity was quantified for low frequency (12-13.5Hz) and high frequency (13.5-15Hz) sigma power. Spindles were also visually counted (frequency 12-15 Hz; duration > 0.5s).
Results: Behavioural Data: To investigate the rate of change in learning across all trials, the regression slopes for improvement in motor performance were compared. Results indicated that habitual and non-habitual nappers improved to the same extent prior to the nap ($t(16)=-1.77$, ns). Following the nap, performance for non-habitual nappers deteriorated, while habitual nappers improved ($t(16)=-2.35$, $p<.05$). Electrophysiological Data: In habitual nappers only, spindle density ($r2=.45$, $t(8)=2.56$, $p=.03$), and high frequency sigma ($r2=.53$, $t(8)=2.79$, $p=.03$), but not total sigma or low frequency sigma, predicted motor performance. There were no significant relationships between spindle activity and motor performance in non-habitual nappers. No other frequency bands (delta, theta, alpha, and beta) predicted motor performance following a nap.
Conclusion: Habitual and non-habitual nappers differed in EEG power density during a nap. Individuals who habitually nap improved on a motor task following a short nap, whereas non-habitual nappers deteriorated on the task. The number of sleep spindles and high frequency sigma activity (13.5-15Hz) uniquely predicted motor performance in habitual nappers but not non-habitual nappers following a nap. Fast frequency spindles may therefore be important for procedural motor learning.

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Improvement and Inertia on Psychomotor Performance Following Short Naps in Healthy Adults: Time of Day Effects

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Introduction: Napping is known to induce both a transient decrease in performance, known as the inertia effect, as well as improvements in psychomotor performance. We analyzed the effect of multiple scheduled naps on psychomotor performance in healthy adults.
Methods: Ten participants (5 Women, 5 Men; mean age: 45.8 +/- 10.4

years) were recorded in a sleep laboratory for three consecutive nights and the two intermediate days. Participants were included if they napped less than once a week, were free of sleep disorders (including excessive daytime sleepiness) based on history and polysomnographic recordings, had no medical conditions interfering with sleep or visuo-motor performance, had no previous experience on shiftwork and kept a regular sleep-wake schedule for seven days before coming to the laboratory. On Day 1, five naps were recorded every two hours, starting at 10h00, according to the standard Multiple Sleep Latency Test procedure except that 20 minutes of sleep was allowed. Participants were tested with the 10 min 4-Choice Reaction Time Test (4CH) immediately before and after each nap. On Day 2, performance was tested at the same time but no naps were allowed. The sequence of Day 1/Day 2 was reversed for half the participants. Conditions interfering with psychomotor performance were ruled out. Variables recorded were Reaction times (RT), number of gaps (RT>1 sec.). and Percentage of error. Means (+/- s.e.m.) were calculated for the entire test, the first and the second half, separately. Results were analyzed using ANOVAs for repeated measures and LSD post-hoc tests.
Results: Participants slept at least 15 minutes on 41 naps out of 50 opportunities, with a mean sleep latency of 10.7 +/- 1.9 min. Psychomotor performance on the first test of Day 1 and the first test of Day 2 were not different from each other, regardless of napping condition. Reversed sequences of napping conditions across days yielded similar results. Compared to the day without naps, performance on the day with naps was characterized by more rapid reaction times (vs. 453 +/- 66 ms vs. 482 +/- 110 ms, $p < .002$) and decreased percentage of error (2.3 +/- 1.2% vs. 2.7 +/- 2.1%, $p < .03$). When performance on the first and the second half of the tests were compared, significant effects were found around the 14h00 and the 16h00 nap: RTs were longer and number of gaps were higher in the first half of the tests following naps relative to before naps. Percentage of error was increased in the first half of the test following the 14h00 nap.
Conclusion: These results show that short scheduled naps objectively increase the psychomotor performance of healthy adult patients but that inertia may affect momentarily this effect particularly in mid afternoon.

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Effects of Moderate Alcohol Intoxication on Sleep EEG Spectral Power in Young Adults: Preliminary Results

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Introduction: Certain sleep stage changes following alcohol consumption are consistent with those seen during recovery sleep following sleep deprivation, including an increase in SWS (stages 3 and 4). Studies have also shown changes in EEG power spectra in NREM sleep following alcohol administration. We have begun to evaluate the effects of pre-sleep alcohol intoxication on sleep EEG spectra in young adults.
Methods: Six healthy adults (ages 21 to 23, mean=22, SD=0.63 years; 1male) kept a fixed 8.5-h sleep schedule for two weeks at home, confirmed by actigraphy and diary. Sleep was then recorded in the laboratory for three consecutive nights (adaptation, placebo, moderate alcohol) on their fixed sleep schedules. The alcohol beverage—vodka (.54 g/kg for men; .49 g/kg for women) mixed with tonic water in a 1:4 ratio—was consumed over a 30 minute period on night 3; the same quantity of placebo beverage—three drops of vodka floated on tonic water—was similarly administered on night 2. Breath alcohol measures were taken at approximately 20-minute intervals in the hour before scheduled bedtime. Breath alcohol concentration confirmed maximum pre-sleep ethanol concentrations of .032 g% to .051 g% (M=. 04, SD=. 01). Sleep stages were scored visually using Rechtschaffen/Kales (1968) criteria. EEG power spectra of REM and NREM sleep (derivation C3/A2) were computed for the entire night, as well as for 2-h intervals across the night beginning at the onset of stage 2 sleep. Differences between individual frequency bins (0.6-30 Hz) in the placebo night vs. moderate alcohol night were assessed on log-transformed power density values.
Results: No significant differences were found between conditions for any sleep stage variable. No consistent differences in all-night power spectra comparing alcohol vs. placebo were found for REM or NREM sleep. The moderate dose of alcohol, however, was associated with a decrease in the high delta/low theta range and an increase in the alpha/low sigma range during the first 2 hours of NREM sleep compared to placebo. In addition, an increase in the low delta range was observed for the final 2 hours of NREM sleep following alcohol administration. No significant differences were present between conditions in REM sleep looking at 2-h intervals across the night.
Conclusion: These preliminary findings point to modest alterations of sleep EEG spectral power, specifically in the first and last parts of the night, when a moderate dose of alcohol is taken near bedtime. We plan to compare the effects of alcohol on sleep EEG spectral components in young people with and without a parental history of drinking problems to determine whether the sleep EEG response to alcohol differs in association with family history.

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Parent-Newborn Co-sleeping in the San Francisco Bay Area

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Introduction: Co-sleeping is the practice of sleeping together, sharing the same room or same bed. Parent-infant bed-sharing has been a controversial practice; proponents claim it facilitates breastfeeding and bonding, while opponents raise concerns about infant safety. Recent studies in the United States indicate that bed-sharing is most commonly practiced by young, single parents with limited educational and financial resources. In addition to infant age, cultural factors strongly influence the practice of bed-sharing, with rates among Asian, Black, and Hispanic mothers being substantially higher than among White mothers. While recent findings suggest that regular bed-sharing is becoming more common in the U.S., rates among older parents (7.5%), more educated parents (7.7%), and White parents (7.2%) remain relatively low. The purpose of this prospective study was to describe newborn sleeping arrangements in a sample of first-time parents in the San Francisco Bay Area.
Methods: As part of a randomized clinical trial, data were collected from childbearing couples during their last month of pregnancy and at one, two, and three months postpartum. This analysis reports on the 72 couples assigned to the control group and first month postpartum data. Mothers used an infant sleep log to record times and locations of their newborn's sleep for 48 hours; these results include specific sleep locations between midnight and 6:00 am.
Results: Parents in this sample were partnered, educated, and had moderate-high incomes. The sample was 60% White, 18% Asian, 14% Hispanic, 6% Mixed/Other, and 3% Black. Sleep logs were completed when the newborn was 19.8 ? 4.4 days old. Of the 72 couples in the control group, 53% reported bed-sharing at least once during the 2 nights of

monitoring, 42% reported bed-sharing during a majority (>50%) of the infant's night-time sleep periods, and 29% reported bed-sharing exclusively. The rates of room-sharing (separate beds) were similar to the rates of bed-sharing. Solitary sleeping was uncommon in this sample of 2- to 4-week old newborns; only 4% always slept in a separate room, 10% slept in a separate room most of the time, and 18% slept in a separate room at least once during the two nights. Rates of bed-sharing, room-sharing, and solitary sleeping were similar across ethnic groups. To minimize potential contamination of the control group, they were not asked about plans for their newborn's sleeping arrangements. Prenatal interview data from the experimental group indicated that only 7% planned to bed-share. Assuming that the rate of planned bed-sharing was similar to the experimental group, most control group parents likely adopted bed-sharing spontaneously, rather than as a traditional cultural practice. For 25% of control couples and 25% of experimental couples, limited household space was a factor in determining where their infant slept.
Conclusion: The rate of bed-sharing was substantially higher than reported in national samples, but similar to that reported for young, low-income mothers living in an inner-city. Furthermore, rates of bed-sharing were consistent across ethnicity. Findings may reflect a growing trend toward bed-sharing, even in cultural groups where it is not traditionally practiced.

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Group Cognitive-Behavioral Therapy for Insomnia: Treatment Outcome and Patient Satisfaction
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Introduction: Cognitive-behavioral therapy (CBT) has been shown to be an effective treatment for chronic insomnia. This study explored the relationship between patients' satisfaction of CBT and clinical outcome measures, and adherence to prescribed behavioral interventions.
Methods: A Clinical case series of 94 outpatients who completed a 7-session group CBT program at Stanford Sleep Disorders Clinic. Data analyses are based on 50 patients who had complete 1-week diary for baseline and for end-of-treatment. At the last group session, patients completed a questionnaires assessing their satisfaction for the treatment, and the extent to which they find various treatment component helful, and their level of adhrance to these treatment components.
Results: 59% of patients rated completely or very satisfied, 35% fairly well satisfied, and 6% somewhat dissatisfied with the treatment. 30.6% reported that the treatment had made their insomnia a lot better. Based on a smaller subset (N=20), on average, patients accomplished 56% of their personal treatment goal. Comparing end-of-treatment to baseline, improvement in SL (19.5 ± 15.2 vs. 35.4 ± 27.84), WASO (36.8 ± 26.3 vs. 65.0 ± 43.5), TST (6.5 ± 1.1 vs. 6.2 ± 1.1), SE (85.2% ± 6.6 vs. 75.2 ± 10.8) and SQ (6.3 ± 1.5 vs. 5.3 ± 1.4), were significant ($p < .03$). These sleep improvement, however, were not related to the degree of adherence to behavioral components (SC and SR; 1.34 ± 0.97) nor to cognitive components (CR; 1.48 ± 1.15). Adherence is correlated with non-specific therapeutic factors and changing attitudes and expectations of sleep.
Conclusion: A significant percentage of patients with insomnia are highly satisfied with group CBT-I. In addition to significantly improved sleep, patients reported that they benefited from the program in terms of improved mood, ability to function, energy, and coping with stress. Improvements in measures of sleep are not correlated with adherence to SC and SR behavioral, and CR interventions. More studies are needed to understand the therapeutic elements in CBT-I that are associated with treatment adherence and clinically significant outcome.

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Sleepiness And Performance In A Cohort Of Medical Residents
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Introduction: Cognitive and motor performance can be impaired with prolonged sleep deprivation. Internal medicine residents are subjected to regular sleep restriction due to their on-call duties. The impact of sleep deprivation on residents and on subsequent patient care is not well documented. Previous literature is conflicting in this area. We wanted to compare performance and vigilance of medical residents with that of control (not on-call) residents. We hypothesize that regular on-call is associated with poorer performance, and that frequent on-call has a greater effect on motor performance and time to recovery.
Methods: Subjects were enrolled for a single period of 28-32 days, which included 4-6 on call nights. Internal medicine residents, ages 18-35 doing regular on-call or non-Internal medicine resident (pathology, endocrinology) with no in house call were included as controls. Subjects were excluded if they had a known sleep disorder or other significant co-morbid illness, were enrolled in another study, were pregnant or unable to give informed consent. Residents were compensated for their efforts ($50-100). All subjects agreed to complete a basic entry-exit survey and wear an activity monitor (Actiwatch® MiniMitter) for the duration of the study. In addition, all subjects performed regular psychomotor vigilance testing using a Palm Pilot version (Walter Reed Army Institute of Research) of the Psychomotor Vigilance Task (PVT). Stanford sleepiness scores (SSS) were recorded at the beginning and end of each 24-hour on-call period.
Results: The preliminary data set includes 7 Internal medicine and 5 control residents. There was no difference in age or gender ($p=0.07$). There was a significant difference in overall mean reaction time (RT) (316 ± 220 vs 255 ± 26 msec, $p<0.0008$) with medical residents having slower times. Internal medicine subjects show no difference in reaction time post-call vs other periods (304 ± 206 vs 320 ± 223 msec, $p=0.71$). Actiwatch data indicates the average time of on-call (presumed) sleep is 280 ± 149 minutes. This significantly differs both from non-call nights and from control subjects [491 ± 129, 480 ± 72 minutes (both $p< 0.0001$)]. Medical residents overall had reduced vigilance. Reactiom times greater than twice the mean RT and minor lapses (>500 msec) were significantly higher in the medical resident group [2.4 ± 4.96 vs 0.49 ± 0.70; 4.49 ± 11.9 vs 0.47 ± 0.98 (both $p< 0.0001$)]. Subjective sleepiness was the same for both groups at baseline (SSS = 2 ± 0.85). Following call as expected medical residents were subjectively more sleepy (SSS = 2.85 ± 0.97, $p=0.002$).
Conclusion: Preliminary data indicates that medical residents have both impaired reaction time and vigilance compared to control subjects. There was no significant change in performance across the study period. Implications for resident well being and patient care remains unclear.

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Pattern of Sleep Diagnoses in Women
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Introduction: Over the years, there has been an increase in the number of media and other campaigns to promote the referral of appropriate patients to sleep disorders centers. Magazines geared toward a female

readership have included many articles on sleep. Given more focus on obesity and risk for sleep-disordered breathing, it was of interest to examine whether the additional attention on quality sleep would translate into a difference in the frequency of types of patients referred to a typical sleep center. To this end, we conducted a chart review to determine the frequency of major sleep diagnoses in women, either self-referred or referred, from 1994-2000. The site was a suburban, accredited center affiliated with a large medical center located 25 miles away.
Methods: Charts from 439 women were analyzed, and the primary diagnosis was recorded from each patient. The diagnoses were based on consultation with sleep professionals (neurologists, psychologist or pulmonologist), most of whom were boarded in Sleep Medicine. The major categories included (1) obstructive and/or positional sleep apnea, hypopnea, and sleep-disordered breathing; (2) snoring; (3) upper airway resistance; (4) insomnia; (5) narcolepsy; (6) restless legs syndrome (RLS) and periodic limb movement disorder; (7) parasomnias (several types); (8) mood and/or anxiety disorder; (9) delayed sleep phase syndrome; (10) poor sleep hygiene (several types); and (11) other.
Results: The number of women seen each year ranged form a low of 43 to a high of 87 patients. The majority of patients were diagnosed with sleep-disordered breathing (27.3%, category 1) or snoring (8.7%). 18.0% were diagnosed with poor sleep hygiene. Only 4.3% were diagnosed with narcolepsy and 7.1% with RLS. Overall, there was no difference in the frequency pattern of diagnoses over the years. However, the percentage of women diagnosed with sleep-disordered breathing was significantly different across the years ($p < 0.01$ by chi-square), with 1997 and 1998 having the highest percentages.
Conclusion: These data suggest that the referral pattern to a general sleep center tends to be stable over the years. It is notable that despite the prevalence of insomnia complaints in the public, relatively few of the patients presenting at this center received a diagnosis of insomnia. Whether this is a function of physician referral patterns, use of medical versus psychiatric benefits, mislabeling on the part of the patient (all sleep problems are "insomnia"), reliance on self-help techniques or other factors should be addressed in future research studies.

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Sleep Satiation II: Effect On MSLT, Reaction Time, And Mood
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Introduction: Many studies of total and partial sleep deprivation have been carried out. However, relatively few studies have investigated the effects of prolonged sleep extension. These studies have shown somewhat conflicting results. Our study of sleep extension challenged subjects to achieve a maximum level of daytime alertness (sleep satiation).
Methods: Fifteen healthy college students reporting minimal daytime sleepiness were studied during baseline, seven nights of sleep extension (mid-satiation), and seven or more additional nights of sleep extension (end-satiation). The number of satiation nights ranged from 13 to 55. MSLT scores, PVT reaction times, and Profile of Mood States scores were measured at baseline, mid-extension, and at end-situation. Nightly sleep amounts were assessed by sleep logs and actigraphy.
Results: There was a significant increase in both sleep log and actigraphy sleep totals during all satiation periods ($p < 0.0001$). The highest sleep totals occurred on extension nights 1-3. Mean sleep log and actigraph sleep times decreased progressively during the satiation period. Extra sleep obtained during the period of sleep satiation was consistently associated with improvements in daytime alertness, reaction time, and mood ratings. MSLT scores increased significantly from the baseline to both mid-satiation ($p < 0.001$) and end-satiation ($p < 0.001$). Seven subjects achieved an MSLT score of 20. Six subjects showed substantial improvements while two subjects who obtained relatively little extra sleep showed little or no MSLT improvement. All eight tabulated PVT values improved significantly during the satiation period with respect to baseline. Average daily POMS vigor and fatigue scores also improved during the sleep satiation period ($p<0.0001$).
Conclusion: Sleep extension to nightly amounts substantially more than habitual sleep times significantly improved MSLT scores, reaction time measures, and mood for subjects as a group. The overall mean improvement in MSLT scores was 8.6. For the subjects who reached an MSLT score of 20, the improvement was 11.8. Given that subjects who reached a score of 20 could not, by definition, show further improvement and that a few subjects started with a reasonably good baseline MSLT score, these results support the conclusion that extended sleep will produce beneficial results. Further, some individuals who report minimal daytime sleepiness appear able to obtain large amounts of extra sleep and to experience improvement in performance and mood even though they may judge themselves to be 'normally' alert prior to extending their sleep.

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Water Gymnastic Increases The Total Sleep Time On Healthy Individuals
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Introduction: Although sleep is an important quality of life marker, there is few studies in literature relating specific aspects of sleep, as for example the Total Sleep Time (TST), to the process of physical conditioning promoted by regular physical activities. This study aims to verify which physical activity (water gymnast, ground gymnast or physical conditioning) promotes an increase in the TST.
Methods: The participants of this study were picked up from academies: Saude Total (Jaboticabal, SP) and Pumping Iron Gym (Sao Paulo, SP), Brazil. They received a sleep diary to be filled in during four weeks. One hundred subjects divided in 3 groups had participated of the study in accordance with activity practiced. Thirty and eight subjects practices Physical Conditioning, PC (36.8±14.46yo), 38 practices water gymnastic, WG (58±14yo) and 24 practices standard gymnastics, SG (aerobic and localized exercises; 34.4±8.77yo). We calculate the mean±standard deviation of the TST for each modality of physical activity. We compared the means with Student T Test.
Results: The subjects that practiced SG presented TST 428,2±54.32min (range: 305.14 to 519.31). The subjects that practiced PC presented TST 460.33±64.92min (range: 343.71to 597.93). The subjects that practiced WG presented TST 483.16±08.61min (range: 319.28 to 780). The subjects that practiced SG presented less TST comparing to the subjects that practiced PC, mean difference 32 min ($p<0.05$). The subjects that practiced WG presented higher TST than SG group, mean difference 55 min ($p<0.05$). There was no statistical difference between WG and PC. WG group wake up earlier (07:30AM±0.048h) than the SG group (07:50AM±0.040h) and the PC group (08:04AM±0.046h). The WG group also sleeps earlier (11:14hPM±0.044h), than the SG group (00:00AM±0.042h) and the PC group (00:02AM±0.050h).
Conclusion: Individuals in the WG group were older and that could be a factor for a reduced TST during the night, but we observed quite the contrary as the WG group have slept 55 minutes more, went to the bed earlier and wake up earlier. Our results support at this time that WG has a direct effect on TST.

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Analysis of Caffeine Data from the National Nurse Fatigue and Patient Safety Study

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Introduction: Much of the data on caffeine use in nurses has been gleaned from two longitudinal and ongoing studies: the 1976 Harvard Nurses Health Study and 1989 Nurses' Health Study II. However, this is the first national study that uses a daily diary to track caffeine intake among nurses on working and non-working days. While caffeine is commonly used as a stimulant among workers in various occupations, the purpose of this analysis was to examine caffeine intake patterns among nurses over a twenty-eight day period.
Methods: Three hundred and ninety-three randomly selected nurses from across the United States, representing 5,317 shifts worked, participated in a larger study of staff nurse fatigue and patient safety. Data collected for 28 consecutive days included information about participants' sleep, scheduled and actual work hours, errors, episodes of drowsiness and actual sleep on duty, and difficulties driving home due to drowsiness. Participants were also asked about their caffeine intake, principally coffee, tea, and other caffeinated beverages, both on working and non-working days during the study period.
Results: Among all nurses, 9.2% (n=36) never consumed caffeine, with 17.8% consuming caffeine on less than 50% of all days and 82.7% consuming caffeine greater than 50% of all days. Fifty-nine percent of nurses (n=232) consumed caffeine everyday. Mean caffeine intake was significantly higher (p=.000) on work days (298.1 mg/day) than on non-work days (233.5 mg/day). Median caffeine intake was also lower (144 mg/day versus 224 mg/day) on shifts where drowsiness was reported on the job, but there was no association between nurses' intake of caffeine and reported drowsiness. There was also a small negative correlation between caffeine intake and increased stress (-.041, p=.003). The age of the nurse correlated to caffeine intake, but the number of years employed as a nurse did not. Caffeine intake did not correlate to whether or not the nurse fell asleep on the job, experienced drowsy driving, or the duration of the main sleep period or total sleep time.
Conclusion: The mean caffeine intake by nurses in this study is slightly higher than the average for the U. S. While caffeine is commonly used as a countermeasure for fatigue and sleepiness, it is unclear if nurses are drowsier on the job than other workers and using more caffeine to combat this symptom. Older nurses appear to consume more caffeine than younger nurses.

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Effects of Pre-Sleep Alcohol on Sleep-Dependent Motor Learning: Preliminary Results

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Introduction: Previous studies show sleep-dependent learning of a motor skill task, demonstrating that significant task improvement after sleep is related to amount of stage 2 sleep. Although alcohol affects alertness and performance, as well as subsequent sleep architecture, its impact on sleep-dependent learning has not been examined. We have begun to test the hypothesis that pre-sleep alcohol administration will adversely affect overnight learning of a motor skill task.
Methods: Six adults (males=1) ages 21 to 23 years (M=22, SD=.63) kept a stabilization schedule of 8.5 hours time in bed for 14 days at home, confirmed by actigraphy and diary. Three in-lab nights on the same schedule followed: adaptation, placebo, and moderate alcohol. On nights 2 and 3, participants were trained on different 5-digit sequence finger tapping tasks (FTT) on a computer keyboard using the non-dominant hand beginning 2-hours before bedtime. Retest on FTT using the same 5-digit sequence as training occurred each morning, 30-minutes after waking. The alcohol beverage—vodka (.54 g/kg for men; .49 g/kg for women) mixed with tonic water in a 1:4 ratio—was consumed over a 30-minute period after task training, ending 60 minutes before bedtime on night 3; the same quantity of the placebo beverage—three drops of vodka floated on tonic water—was similarly timed and administered on night 2. FTT variables included average number of correct sequences (speed) and number of incorrect sequences divided by total number of sequences x 100 (percent errors). Sleep was visually scored in 30-second epochs using Rechtschaffen and Kales (1968) criteria, and variables assessed included stage 2, SWS, and REM sleep as a percentage of total sleep.
Results: Peak pre-sleep breath alcohol concentration on night 3 ranged from .032 g% to .051 g% (M=.04, SD=.01), indicating moderate intoxication at bedtime. No sleep stage variable in this small sample showed a significant night-to-night change. Speed showed overnight improvements in performance for placebo and alcohol conditions, and percentage of errors showed improvement after placebo but not after alcohol on average. Post hoc tests examining whether performance improved more after placebo than after alcohol were not statistically significant, although trends in this small sample were in the predicted direction. Speed showed average improvement of 23% on placebo night versus 15% on alcohol, and percentage of errors showed a 53% decrease on the placebo night versus an average increase of 29% on the alcohol night.
Conclusion: If sleep-dependent learning does indeed depend upon the structure of the intervening sleep episode, then we should expect to see an association of learning impairment with alcohol-associated sleep stage modifications. Analysis of such an association will require a larger sample, and additional data collection is underway. We project that a sample size of 30 participants will be adequate to detect whether pre-sleep ethanol affects sleep-dependent learning on this motor task. Ultimately, we plan to assess whether such effects differ as a function of family history of alcohol problems.

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Sleep in the Population: Socioeconomic and Demographic Predictors of Sleep over 34 Years

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Introduction: Most studies of disordered sleep at the population level have been cross-sectional in nature. Little is known about the persistence of insomnia and short sleep duration over the adult life course, or about the influence of socioeconomic factors on the occurrence of sleep problems. The purpose of this study is to describe the prevalence and pattern

of short sleep duration and symptoms of insomnia in a cohort of adults followed over 34 years, and to assess the role of socioeconomic and demographic factors in influencing these longitudinal patterns.
Methods: The Alameda County Health and Ways of Living Study (ACS) was conducted in order to study the role of various behavioral, psychological, social and demographic factors in the population's health. The study was implemented in 1965 (n=6,928) with a random sampling procedure that recruited a representative sample of the adult, non-institutionalized population of Alameda County, California, and follow-up data collection occurred in 1974, 1983, 1994 and 1999. The written questionnaire included information on frequency of insomnia symptoms and usual sleep duration at all five waves. To the question 'How often do you have any trouble getting to sleep or staying asleep?', respondents indicated 'often', 'sometimes' or 'almost never', and to the question 'How many hours of sleep do you usually get at night?' responses were '6 hours or less', '7 hours', '8 hours', or '9 hours or more'. Descriptive statistics will characterize the persistence of insomnia symptoms (often have trouble) and short sleep duration (6 hours or less) according to the total number and consecutive sequence of repeated responses. The relative odds of increasingly persistent insomnia symptoms and short sleep time compared to the reference group (almost never have insomnia symptoms and 7-8 hours sleep duration, respectively) will be modeled using a series of logistic regression models to assess the role of various socioeconomic and demographic characteristics, including age, gender, race, income, education, and occupation, on persistence patterns. Subsequent models will control for other factors that may be related to sleep problems, including marital status, household density (# people/ # rooms), number and age of children in the household, chronic ailments/impairments, depression, body mass index, physical activity, smoking and alcohol consumption. Random effect growth models will assess the role of predictors that vary over time (such as income) on the odds of repeated measures of insomnia symptoms and short sleep duration.
Results: Preliminary analyses indicate, at baseline (sample mean age 44 years), the prevalence of often having insomnia symptoms was 8.0%; 15.2% had usual sleep duration of 6 or less hours. Frequent insomnia symptoms were more prevalent in women than in men across the 34 year period. Short sleep duration was more prevalent in men than women <30 years old, but more prevalent among women than men = 65 years old.
Conclusion: A substantial proportion of the population reporting frequent insomnia symptoms and short sleep duration at one time point may also experience these symptoms persistently in adulthood. Further longitudinal analyses will shed light on the pattern of occurrence of these characteristics of sleep across adulthood.

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Estimated Average Amount of Sleep Does Not Differ Significantly From Previous Night Sleep Time

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Introduction: Epidemiological studies have determined the average duration of adult sleep is between 7 to 8 hours per night. These studies have largely been questionnaire based and rely on accurate subject estimation of their average amount of sleep. The purpose of this study is to determine if one's estimate of average nightly sleep amount differs significantly from the time reported the night prior to being studied in the laboratory.
Methods: A total of 367 patients (ages 19-86, X=50, Sd=15; 216 male, 151 female) undergoing studies in the University of North Carolina's Sleep Disorders Center from May 2003 to October 2003, estimated their average bedtime and wake time. With these values, an estimated average sleep time (EAST) was calculated. Additionally, patients reported their bedtime and wake time for the previous sleep period. With these values, the previous night's sleep time (PNST) was calculated. Finally, the difference between the two values (EAST – PNST) was calculated.
Results: 367 patients were evaluated with mean EAST and PNST of 8.1 hours (1.6) and 7.9 hours (2.1) respectively with a mean (EAST-PNST) of 0.2 hours. There was no significant difference between males (n=216, EAST 7.9 hours (1.6), PNST 7.8 hours (2.2), EAST–PNST 0.1 hours) and females (n=151, EAST 8.3 hours (1.7), PNST 8.1 hours (2.1), EAST-PNST 0.2 hours). No significant difference was found when subjects were grouped by age: 18-39 years (n=92, EAST 8.3 hours (1.8), PNST 8.3 hours (2.4), EAST-PNST 0.0 hours), 40-59 years (n=179, EAST 7.9 hours (1.6), PNST 7.6 hours (2.2), EAST-PNST 0.3 hours) and 60 years or older (n=96, EAST 8.2 (1.5), PNST 8.1 (1.6), EAST-PNST 0.1). In 181 (49.3%) of the patients, their EAST and their PNST differed by one hour or more. In 75 (20.4%) of the patients, their EAST and their PNST differed by two or more hours.
Conclusion: These results demonstrate that based upon our cohort of North Carolina patients, estimated average nightly sleep amount does not differ significantly from the sleep time reported from the previous night. One limitation of this protocol was its use of sleep study patient instead of "normals", so the results may or may not be applicable to the population as a whole. Anticipating their night in the sleep lab may have affected the quantity of sleep prior to their study. Interestingly, our average PNST of 7.9 hours/night fell within the 7 to 8 hour range generally accepted as the average amount of adult sleep and support previous findings that men, on average, sleep slightly longer than women. Although the average and previous night sleep were close, approximately 50% of individuals demonstrated a difference of greater than one hour. This study shows that both questions of estimated average and prior night sleep need to be asked for patients having sleep studies.

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Sleepiness And Canadian Adolescents: An Integrative Model Relating Sleepiness, Sleep Quality, Sleep Quantity To Daytime Performance

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Introduction: Research has supported the importance of sleep quality and quantity as independent predictors of adolescent daytime sleepiness and has found that sleepiness is significantly related to adolescents' daily functioning, most specifically to mood, hyperactivity and attention. However, research has failed to integrate these findings into a comprehensive conceptual framework and to test simultaneously each of these variables' contributions. Failure to simultaneously evaluate the contributions of these constructs runs the risk of generating spurious findings due to overlap among these factors and potentially sacrifices parsimony. Thus, this study had several goals 1) to test a structural model that integrated findings on the relationships among sleep quality, sleep quantity, daytime sleepiness and factors associated with adolescents' daytime functioning (subjective mood, attention & hyperactivity); 2) to verify previous findings that sleep quality and quantity are significant predictors of adolescent sleepiness and to further differentiate the effects of insomnia from restless sleep; 3) to corroborate research based on American samples that increased sleepiness is related to poorer attention, poorer mood and greater hyperactivity; 4) to use multiple group analysis to determine if the structural model was invariant with respect to sex. It was proposed that 1) daytime functioning would be predicted from a causal chain with daytime sleepiness as a proximal determinant and two factors representing sleep quality (restless sleep and insomnia) as more distal determinants; 2) sleep quality and sleep quantity would

predict daytime sleepiness. Structural equation modelling was employed to evaluate the proposed model, as it permitted simultaneous consideration of its multiple determinants.
Methods: A questionnaire addressing students' sleep patterns, school and extracurricular activities, work involvement, mood, substance use, daytime sleepiness, and symptoms suggestive of primary sleep disorders was completed by 1034 Canadian highschool students (567 female, mean age 16 yrs (SD=1.4)).
Results: The hypothesized model provided an excellent fit to the data, as indicated by the consistently high values for the GFI (.95) and CFI (.97) combined with small values for the RMR (.17) and RMSEA (.03). The X2:df ratio of 1.88 was indicative of an excellent fitting model (< 3 required). The model accounted for a significant amount of variance in the following exogenous variables: 67% in attention, 30% in hyperactivity, and 44% in subjective mood. Daytime sleepiness was a significant predictor of each of the exogenous variables and seemed to be most predictive of greater inattention. Sleep quality was a stronger predictor of daytime sleepiness than sleep quantity. Furthermore, sleep quality exerted its influence on the exogenous variables via both direct and indirect (through daytime sleepiness) pathways. Finally, the predictive power of the two sleep quality latent variables was differentiated by sex. Insomnia was a more powerful predictor of daytime sleepiness for women, whereas, restless sleep was a much better predictor of daytime sleepiness for men. Results from independent t tests indicated that women reported poorer sleep quality on measures of both insomnia and restless sleep (p<.001). Thus, the sex differences present within the model were not simply the result of males reporting more restless sleep and females reporting more insomnia symptoms. Rather, it appears that the symptoms of insomnia have a greater impact on women, and that restless sleep has more detrimental effects for men.
Conclusion: The proposed model fit the data well. Sleep quality was a much better predictor of adolescent sleepiness and daytime functioning than sleep quantity. Sleepiness predicted adolescent daytime functioning and was most highly related to inattention. Results also showed that insomnia symptoms had a greater impact on women, whereas, restless sleep had more detrimental effects for men.

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Levels Of Fatigue And The Intake Of Coffee And Alcoholic Beverages

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Introduction: Recently, we reported a relationship between levels of fatigue and the salience of the physical symptoms associated with exposure to second-hand cigarette smoke. These results suggested that persons with high levels of fatigue responded to their environment in a super-sensitive manner. In this study, we sought to broaden this relationship by measuring the associations between levels of fatigue and persons' typical daily use of coffee and alcohol. Since the self-perception of exhaustion is a common symptom of fatigue, we speculated that compared to persons who scored low on a fatigue scale, persons who scored high on this scale would drink more coffee each day (a stimulant) and use less alcohol (a sedative) as a means of compensating for their feelings of exhaustion.
Methods: To do this, first, from a larger group, we identified 100 undergraduate students (50 men and 50 women) who had scored high (i.e., in the top 20%) on a short form of the Fatigue Impact Scale (This FIS–10) and a group of 50 male and 50 female undergraduates who had scored low on the FIS–10 (i.e. in the bottom 20%). These groups were selected so that they were matched as closely as possible for age, ethnicity, and year in college. Next, for these High and Low Fatigue Groups, we scored their responses to two open–ended questions which asked them to estimate the average numbers of cups of coffee and alcoholic beverages that they consumed each day. The means, standard deviations and the results of the t statistics employed to compare these groups on the daily use of these beverages are included in the following table.
Results: High Fatigue Low Fatigue Bev. M SD M SD t p est.w2 Coffee .83 1.32 .33 .57 3.57 <.001 .055 Alcohol 1.06 2.29 1.55 1.36 1.36 <.100 .004 The data summarized in this table are consistent with our speculations that relative to the Low Fatigue Group, the High Fatigue Group drank more coffee each day (2.54 times more than the Low Fatigue Gorup) and used less alcohol each day (The Low Fatigue Group reported 1.46 times more alcohol consumption than the High Fatigue, but as is noted in the table, the difference in daily alcohol use between these groups did not reach the level required for statistical significance, i.e., p < .05).
Conclusion: Collectively, these data may suggest that the High Fatigue Group's pattern of daily use of these beverages is consistent with what could be viewed as an attempt to control the feelings of exhaustion which typically accompany high levels of fatigue.

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Body Mass Index and Sleep in Normal Sleepers by Gender and Age

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Introduction: There is little research comparing Body Mass Index (BMI = weight to height ratio) and sleep. One study that did compare BMI and sleep concluded that high BMI is a risk factor for disturbed sleep. The same study concluded that female gender is a risk factor, a finding supported by numerous other studies that compared gender and sleep. Research also suggests that advancing age is associated with disturbed sleep. The purpose of this study is to determine if BMI is related to sleep in normal sleepers, and whether any such relationship is associated with gender and age.
Methods: We recruited participants between the ages of 20 and 98 in Shelby County, Tennessee, using a random-digit dialing procedure. Volunteers were paid between $15 and $200 for completing two weeks of sleep diaries and other questionnaires that provided subjective measures of sleep variables such as sleep onset latency, number of nighttime awakenings, wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE), and sleep quality rating. Participants were classified as normal sleepers whose sleep diaries did not satisfy criteria for an insomnia syndrome (sleep latency < 30 minutes and awake time during the night < 30 minutes, for at least 5 nights per week), and those who did not make a subjective sleep complaint such as chronic or non-chronic insomnia, hypersomnia, sleep apnea, periodic limb movements or restless legs, or narcolepsy. We then produced correlation matrices to identify associations between BMI and sleep with respect to gender and age.
Results: In women (n = 175), greater BMI (range = 15.51 to 58.53) was associated with significantly less TST (r = -.190, p < .05) and significantly lower SE (r = -.181, p < .05), but there were no significant associations between BMI and sleep among men (n = 218). In women between the ages of 20 and 29 (n = 38), greater BMI was associated with a significant increase in WASO (r = .444, p < .05) and significantly lower SE (r = -.403, p < .05). In women between the ages of 40 and 49 (n = 35), greater BMI was associated with a significant decrease in TST (r = -.525, p < .01) and significantly lower SE (r = -.466, p < .05). There were no significant associations between BMI, sleep, and age among

men.
Conclusion: Greater BMI in women, but not men, was associated with significantly less total sleep time and significantly lower sleep efficiency. This association was accounted for primarily by women between the ages of 20 to 29 and 40 to 49, as greater BMI was not significantly associated with worse sleep in women comprising any other age group. Interestingly, BMI was not related to worse sleep in women 50 years of age and older.

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Stress, Autonomic Tone and Beta Power are Coupled During NREM Sleep

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Introduction: Our laboratory is interested in the mechanisms that link waking states such as stress and emotional arousal to sleep. In previous studies we have shown that stress is independently linked to increased EEG arousal and heightened autonomic tone during sleep. Importantly, these relationships are seen even in the absence of visually scored sleep disturbances (e.g., poor sleep efficiency). Our studies suggest that the impact of stress and emotional arousal on sleep is more subtle and complex than previously hypothesized. In this study, we sought to characterize the temporal relationship between autonomic tone during sleep and Beta power, which is viewed as an index of heightened cortical arousal. We were also able to evaluate the extent to which acute stress impacts the relationship between autonomic tone and Beta power.
Methods: Participants were 63 healthy undergraduates (mean age = 19 years, 51% female) who spent one night in the sleep laboratory. Prior to sleep, participants were exposed to a speech task (stress group) or control condition. Autonomic tone was measured by autoregressive spectra of EKG interbeat intervals (heart period variability). The ratio of low-to-high frequency power was used to quantify sympathetic nervous system activity, and normalized high frequency spectral power (.15 - .4 Hz/total power) was used as an index of vagal tone. Heightened autonomic tone was conceptualized by increases in sympathetic nervous system activity and decreases in vagal tone. Heart period variability and Beta power (17.0 - 32.0 Hz) were calculated for each successive 2-minute bin across NREM 1 - 4. An autoregressive model was then used to evaluate the temporal relationship between autonomic tone and Beta power (in 2 minute bins) during each NREM period.
Results: Analyses revealed significant relationships between autonomic tone and Beta power during NREM sleep. In each NREM cycle, increases in sympathetic nervous system activity were accompanied by concomitant increases in Beta power (all p values $< .05$). The inverse was true for vagal tone. Increases in vagal tone were accompanied by decreases in Beta power during each NREM cycle (all p values $< .0001$). Significant interactions between experimental group and autonomic tone indicated that acute stress significantly impacted the relationship between vagal tone and Beta power. Acute stress exaggerated the negative relationship between vagal tone and Beta power in all but the first sleep cycle (all p values $< .05$). Analyses of the lagged relationship between autonomic tone and Beta power (T - 1; T + 1) did not reveal consistent relationships among these variables.
Conclusion: Results extend previous research to demonstrate that autonomic tone, as measured by heart period variability, and Beta power are tightly coupled throughout NREM sleep. During each NREM period, increases in Beta power were accompanied by increases in sympathetic activity and decreases in vagal tone. Acute stress amplified the relationship between vagal tone and Beta power in later sleep cycles. This latter observation is consistent with our previous report of blunted vagal tone across the night in response to acute stress. Both sets of results suggest that acute stress can elicit and maintain heightened arousal throughout NREM sleep. We plan to use time series analyses of heart period variability, which allows evaluation of smaller units of time (e.g., 4-second bins), to further characterize the time lag between heart period variability and quantitative EEG during sleep.

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933

Fatigue of Staff Nurses Working in the Hospital Setting

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Introduction: Fatigue is a phenomenon of concern to health care providers because of its implications for safety in the work setting. Fatigue is prevalent in our society and often affects hospital staff nurses who work with rotating shifts in a demanding profession. There has been paucity of research regarding fatigue and its potential effects on nursing roles. This problem is especially important with the current nursing shortage that requires long, exhausting working hours.
Methods: This study examined fatigue relating to judgment and morale in a sample of 26 nurses who work at two small rural hospitals in the Midwest. The research data was collected using a demographics questionnaire, Visual Analog Scale for Fatigue (Lee, Hicks, & Nino-Mucia, 1990), and a Visual Analog Scale for Outcomes (VAS-O). The VAS-O developed by the researchers consists of ratings of judgment and morale that were piloted in this study.
Results: The data was analyzed by paired t-tests and correlation tests. The overall pre-shift fatigue score mean was 33 and the post-shift mean score of this sample of nurses was 77, ($t = -6.99$, $p = .000$). The correlation coefficient of pre-shift fatigue to judgment was -.6706 while the correlation coefficient of post-shift fatigue to judgment was -.5433. The pre-shift judgment mean was 8.15 and the post-shift judgment mean was 6.27, ($T = 3.74$, $p < .001$) showing a significant decrease in the ability to make judgment at the end of the shift. Morale scores were not significantly changed pre-shift to post-shift. Nurses working in the medical/surgical department, compared to a critical care department and general department, showed the greatest increase in fatigue with a pre-shift mean score of 32.66 that soared to a mean of 117.33 for the post-shift score. Nurses working an eight-hour shift showed a rise in their fatigue rating of 20.56 points, escalating from 38.88 pre-shift to 59.44 post-shift; whereas nurses working a twelve-hour shift increased 56.73 points from a pre-shift mean of 30.64 to post-shift of 87.37.
Conclusion: Nurses working longer shifts and nurses working in a medical/surgical department experience greater fatigue. Nurses in medical/surgical departments generally are assigned larger numbers of patients. These findings have implications for staffing patterns. As nurses experience greater fatigue, their ability to make judgments decreased. Decreased judgment may impair the quality of care delivered to patients. Increased feelings of fatigue also may contribute to nurse burnout and impact nurse staff retention. Repeating this study with a larger sample size at several larger hospitals is recommended.

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